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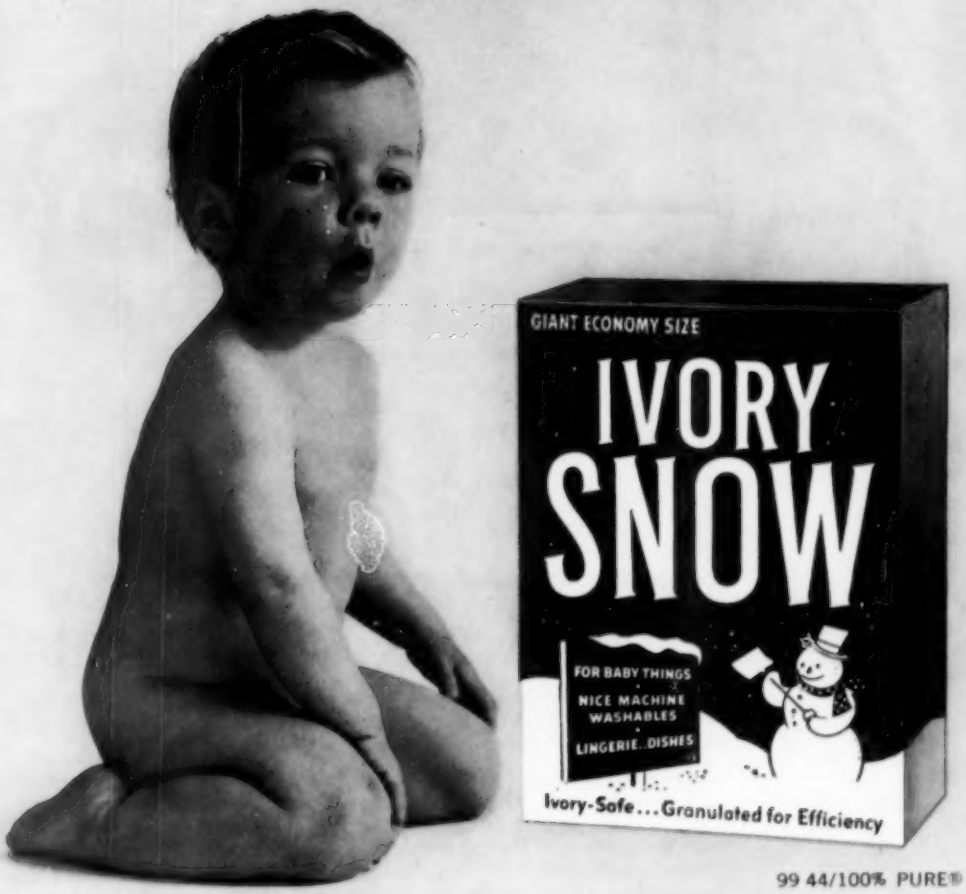

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Staphylococcal Infections in Newborn Infants

III. Colonization of Newborn Infants by Staphylococcus Pyogenes

JACK N. BALDWIN, Ph.D.; MELVIN S. RHEINS, Ph.D.; ROBERT F. SYLVESTER Jr., M.D., and THOMAS E. SHAFFER, M.D., Columbus, Ohio

Introduction

We recently described the bacteriologic investigation and control of an epidemic of staphylococcal infections associated with the newborn nurseries of The University Hospital, Columbus, Ohio.[1] In this epidemic, clinical manifestations were pyoderma, breast abscesses in nursing mothers and infants, and, in a few instances, more serious infections, such as cellulitis, osteomyelitis, pneumonia, and septicemia. More than 50% of the infants admitted to the nurseries during the epidemic developed evidence of infection, and breast abscesses occurred in approximately 30% of the nursing mothers. A single strain of Staphylococcus pyogenes, bacteriophage Type 42B/47C/44A/52/80/81 * was isolated from all lesions. This organism was sensitive to bacitracin, neomycin, chloramphenicol, erythromycin, carbomycin, novobiocin, and oleandomycin † and resistant to penicillin, streptomycin, and the tetracyclines. Practically all infants who were in the nurseries during the epidemic, whether or not they were clinically ill, showed nasal colonization with the "epidemic" strain at the time of discharge from the hospital. Many of these colonized infants who were clinically well when they left the hospital developed infections at home. Among 178 hospital personnel intimately associated with the infants, 7 carriers were identified, all of whom were on full-time duty in the nursery. When all the usual measures failed to control the epidemic, the organism was eradicated from the infant population by the oral administration of erythromycin to all infants for one week, beginning immediately after birth.

Similar epidemics have been reported by Webb,[2] Parker,[3] Colbeck,[4] Rountree,[5] Ravenholt,[6] and Isbister[7] and apparently are appearing with increasing frequency.[8] In each instance these authors reported that specific strains of staphylococci were involved.

Differentiation between similar strains of staphylococci is fundamental to the study of such epidemics and has been accomplished principally by determining bacteriophage type. By the use of this procedure and the determination of sensitivity to antibiotics it has been possible in our laboratories to demonstrate that the strains of S. pyogenes incriminated in 41 similar but widely separated outbreaks occurring during the past two

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From the Departments of Pediatrics and Bacteriology, The Ohio State University.

This study was supported by grants from Eli Lilly and Company and the United Health Foundation of Metropolitan, Lorain, Ohio (O. S. U. Development Fund Projects, Nos. 5196 and 5688).

* Phages 80 and 81, not available in 1954, subsequently were shown to lyse this strain.

† Subsequent to the first report, this strain was found to be sensitive to novobiocin and oleandomycin.

years were identical to the organism responsible for the epidemic in Columbus.[8]

The present investigation was undertaken to determine and examine the factors associated with the colonization of infants by S. pyogenes. Since infants are continually exposed to many different strains of potentially pathogenic staphylococci during their stay in the hospital, it is important to understand the source and modes of transmission of staphylococci acquired during the first days of life.

Methods and Materials

Three nurseries at University Hospital, all on the same floor, were included in the present study. Nasal cultures were obtained daily from all infants in one nursery, containing 15 bassinets, while associated nursing personnel were cultured weekly. In the remaining nurseries (40 bassinets), nasal cultures were obtained from infants at the time of discharge; nursing personnel in these nurseries were cultured monthly. Nasal cultures were obtained at monthly intervals from other personnel who came into contact with the infants. In addition, the skin of the inguinal region of infants was cultured periodically and on several occasions various areas of the nursery environment were sampled. Techniques for the isolation and characterization of coagulase-positive staphylococci have been described previously.[1] These included identification of distinct strains by bacteriophage typing and determination of antibiotic sensitivity. Strains which could not be typed by the routine test dilution of bacteriophage were tested with undiluted bacteriophage suspensions.[9,10]

Results

Over a period of seven and one-half months (April 20 through November, 1955) 1546 nasal cultures from 435 hospital personnel, 3055 nasal cultures from 1232 infants, and 370 nasal cultures from 265 mothers were obtained (Table 1). Of these, 374 from hospital personnel, 762 from infants, and 85 from mothers yielded coagulase-positive staphylococci. Determination of antibiotic sensitivity (penicillin, chlortetracycline, streptomycin, chloramphenicol, erythromycin, bacitracin, carbomycin, neomycin, and novobiocin) and bacteriophage type (36 bacteriophages) differentiated these coagulase-positive staphylococci into 99, 54, and 75 separate and distinct strains in the three respective groups.

TABLE 1.—*The Distribution of Coagulase-Positive Staphylococci and Distinct Strains Among Hospital Personnel, Infants, and Mothers*

	Persons Cultured, No.	Cultures, No.	Coagulase Positive Cultures, No.	Distinct Strains, No.
Personnel	435	1,176	374	99
Infants	1,232	3,055	762	54
Mothers	265	370	85	75
	1,932	4,601	1,221	

Of the 1221 coagulase-positive cultures isolated, 79.7% were typable with use of the routine test dilution of bacteriophage; 18.2% were typable with full-strength phage, and 2.1% were not typable with the bacteriophage used in these studies. The percentage of typable cultures (97.9%) is comparable to the 95% typed by Bynoe and considerably higher than the 60% to 80% reported by other investigators.

From the beginning of this study is was obvious that the number of infants colonized by S. pyogenes was considerably lower than were the numbers reported by other investigators. This is shown graphically in Figure 1, in which the rate of colonization of infants at University Hospital is compared with the rate reported by Cunliffe.[12] Carrier rates beyond six days were not determined, since relatively few babies remained in the nurseries after this period. As may be noted, only 30% of the infants born at University Hospital were nasal carriers of S. pyogenes on the sixth day after birth, as compared with 96% of the infants in Cunliffe's study.

Since October, 1954 (except where omitted for experimental reasons), infants in the nurseries have been bathed soon after birth and every other day thereafter with a liquid detergent containing 3% hexachlorophene.‡ Figure 2 clearly demonstrates the marked increase in the percentage of infants colonized with S. pyogenes when "dry" skin care was instituted in one of the nurseries. On six separate days, as high as 100% of

‡ Hexagerm, Huntington Laboratories, Philadelphia.

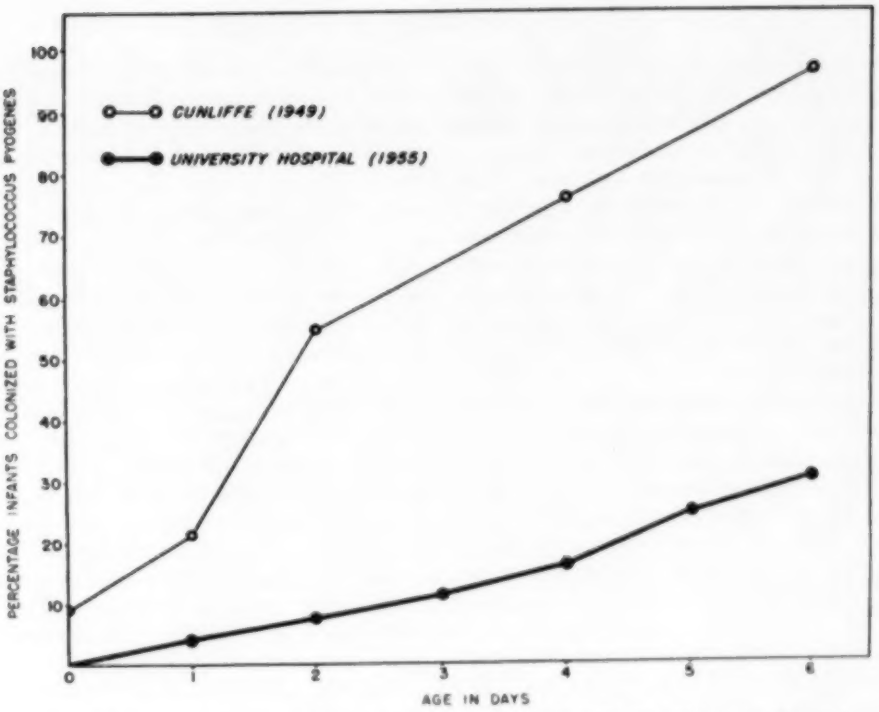
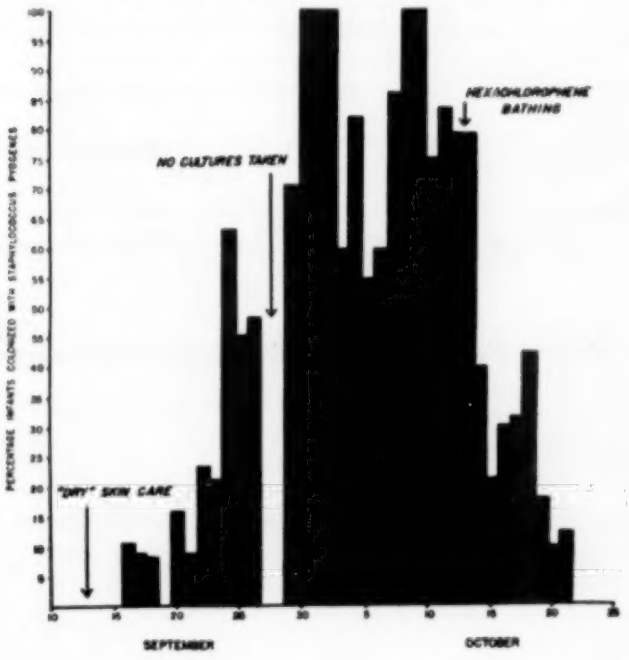


Fig. 1.—Comparative rate of nasal colonization (Cunliffe,[12] 1949; The University Hospital, 1955).

Fig. 2.—The influence of the type of skin care on nasal colonization of infants.



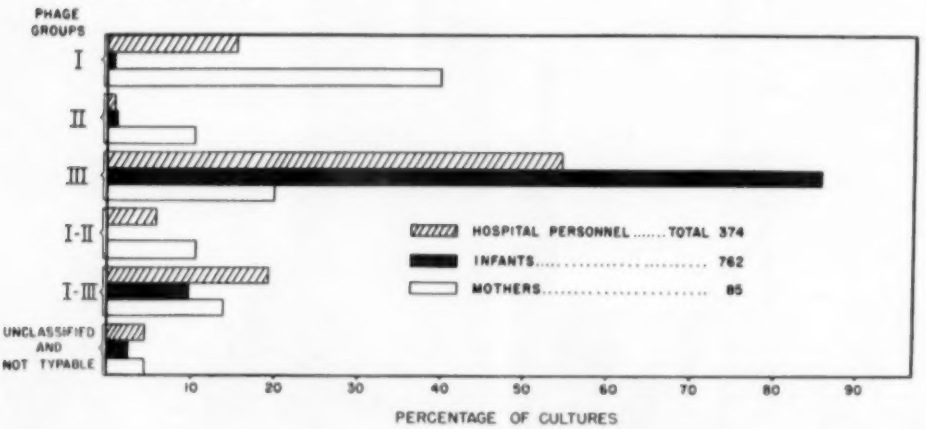
the infants were colonized when this skin-care procedure was followed; 65% of these infants also showed colonization of skin in the inguinal region, as compared with only 16% among infants who received "hexachlorophene baths" routinely. Immediately following the reinstitution of "hexachlorophene baths," a sharp decrease in the number of infants colonized was observed.

When this experiment was repeated in another nursery, the incidence of nasal colonization and the effect of hexachlorophene were essentially the same as depicted in Figure 2. However, during the second period of "dry" skin care 90% of the infants showed colonization of the inguinal region, as compared with the 65% in the first study. In an additional investigation, the failure to obtain similar results was attributed to the marked and significant differences in the capacities of various strains to colonize the newborn. The importance of this observation is discussed in a later section of this report.

As was anticipated from the results of other investigators,[3,12-15] the strains of S. pyogenes isolated from infants were in most instances the same as those isolated from the nasal cultures of the attending nursery personnel. Rarely were infants colonized by strains harbored by personnel in the obstetrical and pediatric services who had not had prolonged contact with the infants. Only 1 mother of the 265 cultured was found to be the source of a strain that colonized infants. Therefore, routine culturing of mothers was discontinued at the end of the second month of the study.

Figure 3 shows the distribution of the 1221 cultures of S. pyogenes according to the source of isolation and the bacteriophage group. The cultures were categorized into phage groups according to the classification of Williams.[16] As can be noted, staphylococci belonging to phage Group I were most prevalent among mothers, whereas staphylococci in Group III predominated in infants and hospital personnel. Although a relatively large number of staphylococci isolated from personnel were in Group I (15.5%) and Group I-II (6%), only 1.3% of isolates from infants were in Group I and none were in Group I-II. These results are in accordance with the findings of many investigators[11,17-20] who have shown that strains of S. pyogenes in Group III are most frequently isolated from hospital personnel and patients. Interestingly, 96% of the cultures isolated from infants were resistant to one or more of the commonly used antibiotics. This was not surprising, since numerous authors have reported that resistance to antibiotics occurs most commonly among strains of S. pyogenes in

Fig. 3.—Distribution of S. pyogenes among hospital personnel, infants, and mothers according to bacteriophage groups.



phage Group III. A detailed analysis of antibiotic sensitivity, bacteriophage type, and physiologic characteristics of the 1221 cultures isolated will be reported in a later paper.

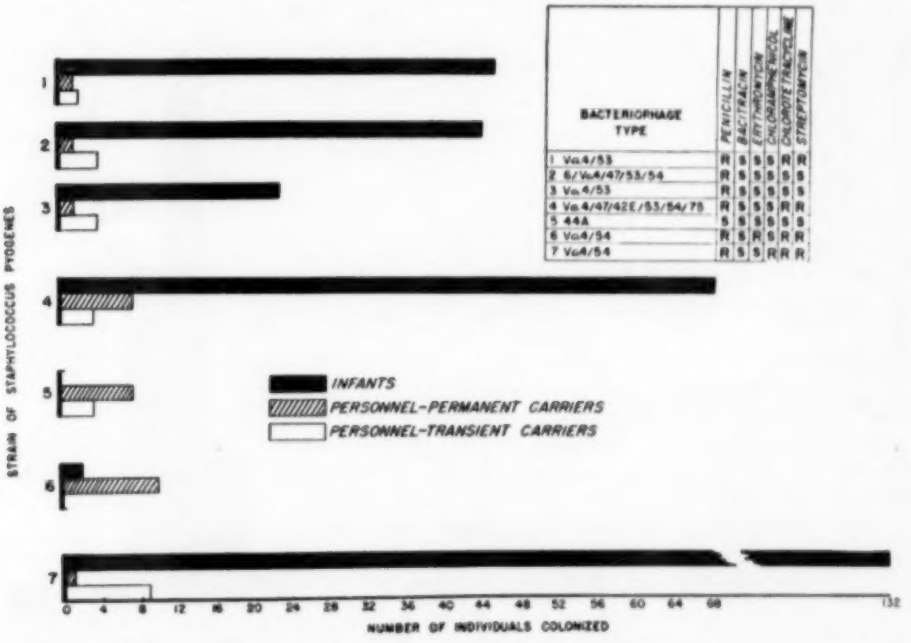
Although a total of 197 distinct strains of S. pyogenes were detected during the course of this study, only 54 different strains were isolated from the 1232 infants cultured. It is noteworthy that five of these strains accounted for 75% of the colonization; one strain alone accounted for 30% of the coagulase-positive staphylococci isolated from the newborn. In four instances strains harbored by nursing personnel colonized only one infant, and in seven instances a particular strain colonized only two infants. Forty-five strains carried by hospital personnel were never detected in the newborn. However, only 7 of those 45 strains were carried by personnel who worked in the nurseries and had prolonged contact with infants. Contrary to the above findings, 24 distinct strains isolated from the newborn were never detected among the hospital personnel.

Some of the typical relationships between the carrier state in infants and personnel are shown graphically in Figure 4. Strains 1, 2, and 3 were responsible for 25% of the colonization of all infants. A single permanent carrier § of each of these strains was detected among the nursing personnel. These strains appeared in the infant population only after the carrier was present in the nursery and disappeared abruptly when the permanent carrier was removed. After the strains became established in the nurseries, transient carriers ‖ appeared, but only among the nursing personnel who had prolonged contact with the infants. In contrast, there were seven permanent carriers of

§ Permanent carrier is defined as a person from whom the same strain of S. pyogenes is consistently isolated in the absence of contact with another source of the strain.

‖ Transient carrier is defined as a person who harbors a strain and for only short intervals and then only when in contact with another source of the same strain.

Fig. 4.—Relationships between the strain of S. pyogenes, the rate of nasal colonization of infants, and the permanent and transient carrier state in nursing personnel.

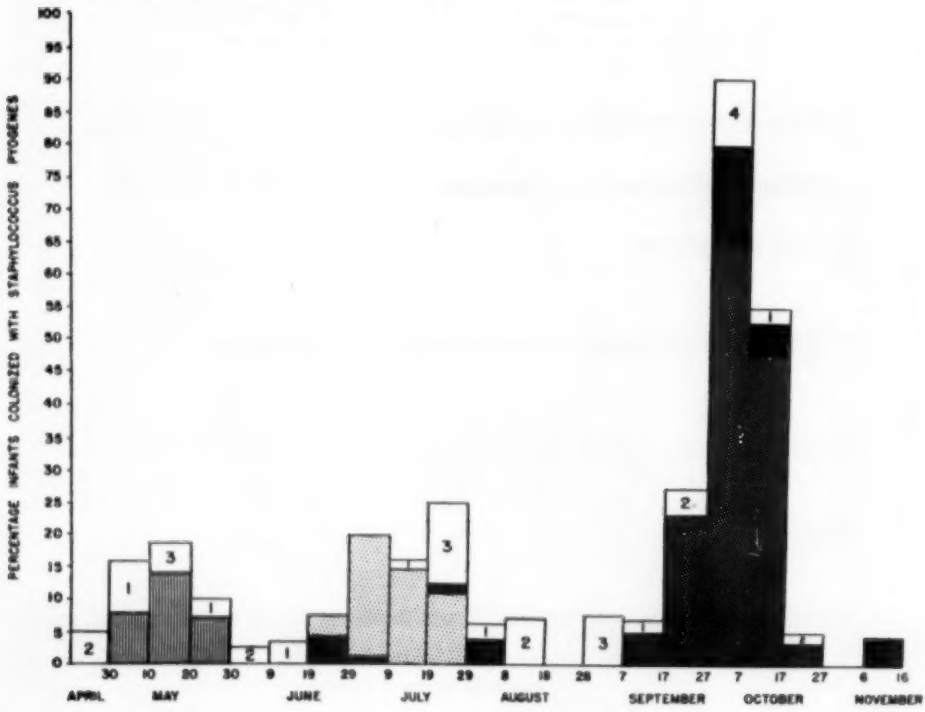


Strain 4. One or more of the permanent carriers of this strain were always present in the nurseries, and infants were colonized at a low rate throughout the period of the investigation. Strain 5 failed to colonize a single infant, even though permanent carriers were present in the nurseries for a period of four months. The three transient carriers were student nurses who harbored the strain only at the beginning of their training period in the nurseries.

Strain 6 in Figure 4 depicts the results of a special experiment wherein an attempt was made to prevent colonization of infants by strains of S. pyogenes resistant to erythromycin. Eleven permanent carriers of erythromycin-resistant strains were detected and immediately removed from close contact with the newborn infants. It is of interest that 10 of these persons carried the same strain, phage Type Va4/54. The effectiveness of removing personnel from nurseries as a means of reducing dissemination of a particular strain was demonstrated by the observation that only two infants were colonized by this strain and none of the nursing personnel became transient carriers.

The observations described above pertained to nursery populations on a strict regimen of "hexachlorophene bathing." During the latter part of September, when "dry" skin care was experimentally introduced in one of the nurseries, a distinctly different strain of S. pyogenes appeared. In a relatively short time this organism, Strain 7 in Figure 4, was isolated from 60% of the infants in the nursery. Even though the permanent carrier who was initially present in the nursery was transferred shortly after the strain appeared, this strain persisted in the infant population at a high rate for 15 days without a demonstrable carrier among the nursing personnel.

Fig. 5.—Incidence of predominating strains of S. pyogenes colonizing infants during a seven-and-one-half-month period.



The importance of including sensitivity to antibiotics in conjunction with the bacteriophage type is shown in the Table accompanying Figure 4. Strains 1 and 3, phage Type Va4/53, predominated in different nurseries during the same month. When they were first detected, it was readily apparent that they were different strains, since one was susceptible to chlortetracycline and streptomycin while the other was resistant to these antibiotics. Likewise, it was possible to designate Strains 6 and 7 (phage Type Va4/54) as distinct strains because of their different susceptibility to erythromycin and chloramphenicol.

The data represented in Figure 5, obtained from one nursery, are typical of the other two nurseries in showing the rate and extent of nasal colonization of infants by different strains of S. pyogenes during a period of seven and one-half months. The four predominant strains, designated by either the solid or the cross hatched areas in the bars, were responsible for 75% of the colonization. Although the other 17 strains are not specifically designated, the number of different strains isolated and the aggregate incidence of these strains during a 10-day period are shown in the clear areas of the bars. Three of the predominating strains appeared and disappeared abruptly, whereas the fourth strain was present intermittently throughout the last five months of the study. The high incidence of colonization during the latter part of September and October occurred after "dry" care was experimentally introduced in this nursery.

The strain that predominated during the month of May deserves special mention, since it represents the only instance in which the permanent carrier of a predominating strain was not found in the nurseries. After a careful reexamination of all personnel in the pediatric and obstetric services, this strain was finally traced to an anesthetist in the delivery room. The abrupt disappearance of this strain from the infant population occurred following her transfer from the obstetrical service.

TABLE 2.—*The Incidence and Bacteriophage Type of Strains of Staphylococcus Pyogenes Isolated from Transient Carriers Among Nursing Personnel*

Nurse	Cultures, No.	Coagulase-Positive Cultures, No.	Bacteriophage Type
1	25	1	44A/47/53/54
		1	Va4/53
		1	Va4/54
2	38	1	44A/47/53/54
		1	Va4/53
		2	Va4/54
3	26	1	Va4/54

It is significant that the transient carriers of four of the five most predominant strains were, with but one exception, persons who were colonized by these strains after they became established in the nurseries and who harbored these strains only during the time the strains predominated in the infant population. This relationship is exemplified in Table 2, with data obtained from the nursery in which the nursing personnel were cultured at weekly intervals. As may be noted, seven coagulase-positive cultures, comprising only three bacteriophage types, were isolated from the three nurses listed. In each instance the coagulase-positive cultures were isolated from each of these nurses at the time the same strains occurred most frequently among the infants as shown in Figure 5.

Comment

During the principal part of this investigation, the strains of S. pyogenes isolated from the nasal mucosa of newborn infants were heterogenous and, as has been demonstrated by Barber,[21] were identical in most instances with the strains carried by some of the nursing personnel. Even though the infants came into intimate contact with the mothers during their stay in the hospital, the mothers were not the immediate source of colonization of the infants. This is in agreement with the findings of Parker,[3] Cunliffe,[12] Rountree,[13] and Barber.[21]

Throughout this study we have been impressed by the marked differences in the capacities of the various strains of S. pyogenes to colonize infants. This was dem-

onstrated by the observation that only five strains were responsible for 75% of the colonization and by the additional finding that other strains constantly present among the nurse personnel either failed to colonize or colonized only one or two infants. Under the usual circumstances only a single strain predominated at any one time in a nursery. Upon transferring the carrier of the predominating strain to a different nursery, that strain would disappear from the infants in the first nursery and reappear in the other and a new strain would appear and predominate in the nursery from which the carrier had been removed (see Fig. 5). This indicates that, under a regimen of "hexachlorophene bathing," the predominating strains were incapable of being perpetuated in the infant population in the absence of a permanent carrier to constantly infect new infants. Should such an organism possess sufficient pathogenicity to cause clinical infections, the cases probably would be sporadic and disappear with change in personnel.

One strain of S. pyogenes, easily recognized because of its distinctive resistance to chloramphenicol, exemplified what may happen when an organism with a high capacity to colonize becomes established in a nursery where "dry" skin care is practiced. This organism rapidly colonized 60% of the infant population despite the fact that seven other strains were present at the same time in both infants and nursing personnel. Even in the absence of a recognized permanent carrier among the nursery personnel, this strain maintained itself in the newborn population apparently by infant-to-infant transmission. Similar instances of propagation from infant to infant have been reported previously by Shaffer [1] and Parker [3] and have been shown to play an important role in epidemics of staphylococcal pyoderma. It was fortunate that the chloramphenicol-resistant strain, although a good colonizer, lacked the capacity to initiate infection, since conditions conducive to the rapid spread of an epidemic were present during the period of "dry" skin care. Had this strain possessed the pathogenic potential of Strain 42B/47C/44A/52/80/81, which was responsible for the epidemic at The University Hospital in 1954,[1] another serious outbreak probably would have occurred.

The marked increase in the rate of nasal and skin colonization observed in infants who received "dry" skin care demonstrates the effectiveness of bathing with a detergent solution containing hexachlorophene for preventing infant-to-infant transmission of S. pyogenes. In the absence of a permanent adult carrier, the chloramphenicol-resistant strain was completely eliminated from both the infant population and the nursery personnel within 10 days after reinstitution of hexachlorophene baths. It may be that the high colonization rates reported by Cunliffe,[12] Torrey,[22] and Rountree [13] (80% to 100% of the infants colonized by the sixth to eighth day of life, as compared with 30% at University Hospital) reflect infant-to-infant transmission under conditions similar to the "dry" skin care experiment described above.

A comparative survey of the distribution of S. pyogenes in the nursery environment during periods of "dry" skin care and at times when "hexachlorophene bathing" was practiced revealed great differences in the number of organisms present. For example, during the periods of "dry" skin care, S. pyogenes was isolated from crib railings, liners, and mattresses and articles that were commonly handled by nursing personnel. Surfaces on which bedding lint collected invariably yielded S. pyogenes. During periods when "hexachlorophene bathing" was practiced, significantly fewer organisms were isolated from these same areas. It would appear that when a strain has become established in a nursery where "dry" skin care is practiced, inhalation of desiccated air-borne vernex or blanket lint contaminated with staphylococci results in an increased rate of nasal colonization. Hexachlorophene bathing when properly performed appears to have a twofold action: (*a*) the mechanical

removal of vernix before it becomes dry and air-borne and (*b*) the prevention of skin colonization through its local antibacterial action.

The role of the transient carrier as a responsible source of staphylococci which colonize infants cannot be completely assessed from our data. Since most carriers were persons who harbored relatively few coagulase-positive staphylococci for short intervals, and then only when a particular strain predominated in the infant population, they probably played a minor role. However, the high incidence of transient carriers observed in this study also occurs during epidemics of staphylococcal infections in nurseries.[1] Although removal of the permanent carrier from contact with infants is necessary for ultimate control of such epidemics, removal of all carriers is not necessary if antibiotic prophylaxis is used to prevent colonization of causal strain in the newborn population. As was observed in this study and in an epidemic,[1] when the prevailing strain disappears from the infants the transient carrier state among nursing personnel also disappears. The permanent carrier then can be readily detected and removed from contact with infants and the prophylactic administration of the antibiotic can be discontinued without disrupting the operation of the nursery.

Summary

The distribution of Staphylococcus pyogenes in infants and hospital personnel was studied over a period of seven and one-half months.

Strains isolated from infants were, with but few exceptions, identical with strains isolated from the permanently assigned nurse personnel.

Seventy-five per cent of the colonization of infants by S. pyogenes was accounted for by five distinct strains, as determined by bacteriophage typing and pattern of sensitivity to antibiotics.

During periods when hexachlorophene bathing was routinely practiced, the rate of infants' nasal colonization was significantly lower than that reported by other investigators.

The deliberate introduction of the "dry" care technique resulted in a marked increase in the rate of nasal and skin colonization.

The significance of the permanent and transient carrier state among nursery personnel is discussed.

John A. Donahue, M.Sc., and Mrs. Virginia Geyer gave technical assistance.

Department of Bacteriology, The Ohio State University (10).

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CORRECTION

In the article "Transient Dysproteinemia in Infants," by Dr. Robert A. Ulstrom et al., in the May issue of the Journal, the second footnote to Table 2 (p. 539) should read as follows:

$$\text{BCC} \times \frac{\text{plasma albumin or globulin (gm. per 100 cc.) in each infant}}{\text{average plasma albumin or globulin (gm. per 100 cc.) in normal infants}}$$

On page 541 the last line of the footnote to Table 3 should read as follows:

$$\sigma_s^2 = \frac{\Sigma(\text{data value} - \text{mean of data values})^2}{n-2}$$

Nephrosis in the Newborn Infant

A Syndrome Difficult to Explain by Existing Theories of Etiology

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The nephrotic syndrome is an easily recognized condition which is manifested by edema, albuminuria, hypoalbuminemia, and hyperlipemia. The characteristic histological lesion consists of thickening and splitting of the basement membrane of the glomerular tufts with secondary tubular degeneration and lipoid deposition.[1] Renal-clearance studies have shown variable results in the acute phase of the disease and moderately to greatly diminished function in the chronic stages.[2,3] The disease is commonest between 18 months and 4 years, although occasional cases are seen in other age groups. We have had the opportunity recently to study an infant who developed the first signs of nephrosis at 15 days of life. This is the third such case reported[4,5] of the nephrotic syndrome in the neonatal premature infant and the first in which renal-clearance measurements have been made during the course of the disease process. Such a case may contribute information as to the etiology of the nephrotic syndrome in terms of modern immunologic concepts.

Methods

The renal-clearance techniques which were used were similar to those reported by Barnett et al.[6] for premature infants. Glomerular filtration rate (GFR) was measured as the clearance of inulin, and effective renal plasma flow (ERPF), as the clearance of sodium *p*-aminohippurate (PAH) at low plasma levels. With each study three 30-minute clearance periods were measured during a continuous intravenous infusion of the materials by means of a Bowman pump. Inulin was determined by the method of Roe et al.,[7] and PAH by the method of Smith et al.[8] The concentrations of albumin and γ-globulin in serum and urine were measured immunochemically by the specific quantitative precipitin method for protein determination as described by Kabat and Mayer.[9]

Report of Case

A girl was born by uneventful, spontaneous vertex delivery at Middlesex Memorial Hospital, on Nov. 18, 1955. Although the expected date of confinement was Nov. 25, 1955, the birth weight was only 2000 gm. The mother was a 25-year-old white primigravida whose past medical history and pregnancy were unremarkable. No hypertension or edema was noted. Her serology was negative; blood, Type A and Rh-positive. The infant cried spontaneously and seemed to do well in the nursery. She was started on the stock evaporated milk formula at 24 hours of age, and her weight gain and feeding habits seemed unremarkable. The only medication given was 2.5 mg. of vitamin K intramuscularly. On the 15th day of life edema of the left eyelid and abdominal distention were noted. She was discharged on the following day, weighing 2330 gm. At home, feedings were taken poorly and there was increasing edema, involving both eyelids, legs, and arms. At 23 days of age twitching of the face and extremities was noted. She was then seen by one of us (A. T.) for the first time and was admitted to the Middlesex Memorial Hospital for diagnostic studies.

Weight on admission was 2750 gm.; length, 46 cm.; head circumference, 33 cm.; chest circumference, 28 cm. She was a thin alert infant with generalized pitting edema, most pronounced on the eyelids, hands, feet and lower abdomen. There were clonic convulsive movements of the face and extremities. The abdomen was tense and markedly distended, with no shifting dullness. No abdominal organs were felt. Color was good, with no icterus. Blood pressure was 80 systolic by auscultatory method. The anterior fontanelle was soft and

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TABLE 1.—*Representative Blood Chemistry Values* *

Age	TP, Gm./ 100 Ml.	A, Gm./ 100 Ml.	G, Gm./ 100 Ml.	Chol. Mg./ 100 Ml.	Na, mEq./ L.	K, mEq./ L.	NPN, Mg./ 100 Ml.	FBS, Mg./ 100 Ml.	CO_2, mEq./ L.	Cl, mEq./ L.	Ca, Mg./ 100 Ml.	P, Mg./ 100 Ml.
23 days	2.6	0.9	1.7	348	134	4.0	22	53	20	...	8.3	5
27 days	2.5	0.8	1.7	360	135	4.9	27	...	...	...	...	...
45 days	2.5	0.8	1.7	370	130	4.2	40	...	...	106	9.4	5
6 mo.	2.9	1.0	1.9	480	145	4.4	29	70	16	...	...	...
7 mo.	2.0	0.7	1.3	439	...	...	...	...	...	...	...	...
9 mo.	2.4	0.4	2.0	1773	118	6.2	171	...	...	98	7	8

* TP, total protein; A, albumin; G, globulin; Chol., cholesterol; NPN, nonprotein nitrogen; FBS, fasting blood sugar.

measured 4 cm., and there was separation of the saggital suture. Funduscopic examination showed no abnormalities. There was a soft systolic murmur along the left sternal border, transmitted to the axilla.

Laboratory Data.—Nose, throat, urine, and blood cultures were unremarkable. Repeated urinalyses showed 4+ albumin (heat and acetic acid method), specific gravity of 1.010 to 1.026, and no reducing substance; the spun sediment revealed 2 to 10 RBC and 0 to 5 WBC per high-power field. Hemoglobin was 13.5 gm. per 100 cc.; RBC, 4,200,000 per cubic millimeter; WBC, 9400 per cubic millimeter, with a normal differential count. The sedimentation rate (corrected) was 15 mm. per hour. Chemical analyses of the serum were typical of the nephrotic syndrome, showing hyperlipemia and hypoproteinemia (Table 1). Serum γ-globulin levels on the 25th and 60th days of life were 275 and 200 mg. per 100 cc., respectively. The determination of serum protein concentrations by paper electrophoresis showed changes typical of the nephrotic syndrome, namely, reduced albumin and γ-globulin, normal α-globulin, and greatly increased β-globulin. Antistreptolysin titer of both mother and baby one month after delivery was less than 12 Todd units (normal is less than 200 units). Urine and blood chemical analyses on the mother were normal two and four weeks after delivery.

On admission, lumbar puncture and subdural taps were not remarkable. Roentgenograms of the chest showed no lung pathology, and the heart was normal in size and configuration. X-rays of the skull showed marked separation of all the sutures.

Treatment and Course.—The patient was treated with phenobarbital, low-sodium milk (Lonalac), and tetracycline. The intermittent convulsions ceased on the sixth hospital day, and the weight fell to 2340 gm. On the 19th hospital day the microhematocrit value fell to 25% and a transfusion of 40 cc. of whole blood (16 cc. per kilogram) was given. Within two days weight rose from 2600 gm. to 2925 gm.; head circumference increased from 34 cm. to 36.5 cm., and twitchings resumed. This course of events was repeated with subsequent transfusions. Renal-function studies were done by one of us (F. G.) on the 25th and 60th hospital days. The results presented in Table 2 revealed relatively normal renal function early in the course of the disease, with some deterioration of function several weeks later. In addition, the protein clearances were elevated early in the disease and were markedly elevated several weeks later.

On the 25th hospital day (7 weeks of age) the infant was started on prednisolone, 4 mg. every six hours. Although weight dropped to 2375 gm. on the ninth day of therapy, with loss of all obvious edema, there was no subsequent improvement of the proteinuria, hyperlipemia, and hypoproteinemia. Therapy was maintained for 21 days, when a pulmonary infection caused the gradual withdrawal of the prednisolone over an eight-day period. Final weight was 2100 gm. Serum proteins and cholesterol and albuminuria remained essentially unaltered. Blood pressure was 70 systolic. The patient was discharged on the 105th hospital day, unimproved, weighing 2500 gm.

While at home she was maintained on prophylactic tetracycline, iron, vitamins, and a low-sodium diet.

At 6 months of age she was readmitted for another course of steroid therapy because of

TABLE 2.—*Renal Clearance Measurements* *

Age, Days	GFR (C_{in})	ERPF (C_{PAH})	C_{ALB}	C_{GG}	$\frac{C_{ALB}}{C_{IN}}$	$\frac{C_{GG}}{C_{IN}}$
48 (25th hos. day)	Absolute value 5.5, corrected value 48	43.4 536	0.084 1.04	0.019 0.146	0.015	0.002
83 (60th hos. day)	Absolute value 3.5, corrected value 43	42 518	0.096 1.18	0.028 0.346	0.028	0.008

* Absolute value corrected to 1.73 square meters of body surface area. C, clearance; ALB, albumin; GG, γ-globulin; IN, inulin; PAH, β-aminohippuric acid.

persistance of the albuminuria and edema. Weight was 2900 gm. She was obviously grossly retarded in development. Her cry was that of a newborn infant. She appeared to be blind and did not smile, grasp, or reach. The optic discs were extremely pale. She received 15 mg. of repository corticotropin injection U. S. P. (ACTH Gel) daily for 12 days. Again, although her weight fell to 2600 gm. with cessation of therapy, there was no alteration of her clinical course or laboratory data. A roentgen survey of her extremities at this time disclosed severe generalized osteoporosis and completely absent carpal centers.

At 8 months of age her clinical course changed in that ascites requiring repeated paracenteses became the principal problem of management. At 9 months of age she was admitted for the last time, because of lethargy, hypothermia, and refusal of feedings. She died a few hours after admission, with obvious uremia. Blood and spinal fluid cultures were negative.

Pathologic Findings.—Autopsy was performed three hours after death. Positive findings were limited to the liver, gallbladder, kidneys, and spleen. There were no venous thromboses. The kidneys weighed 20 gm. each; the capsule stripped easily. The cortex was well demarcated from the medulla. Microscopically, the glomeruli showed increase in number and size of epithelial cells in areas of basement membrane alterations. There was marked thickening and some splitting of the basement membrane. There were no crescent formations or adhesions. Endothelial cells were not increased in number. The tubules showed varying degrees of cytoplasmic granularity and vacuolization with loss of nuclei. Hyaline and granular casts were noted. Small foci of calcification were present throughout the parenchyma. Stain with Sudan IV showed fat in the interstitial cells, tubules, and tubular cells. The liver weighed 70 gm. and was dotted with numerous discrete gray lesions, which proved to be hemangiomata on section. The gallbladder contained a single cholesterol stone. The spleen weighed 12 gm. and appeared grossly normal. The sinusoids contained relatively few cellular blood elements. In many areas they were lined with large ovoid cells with vacuolated cytoplasm and small vesicular nuclei. These cells stained positively with Sudan IV. The adrenals, brain, pancreas, and thyroid were unremarkable. No parathyroid tissue was identified. Pathological diagnosis: lipoid nephrosis, nephrocalcinosis, cholelithiasis, hemangiomata of the liver, ascites, and emaciation.

Comment

Occasionally the nephrotic syndrome may occur in association with certain other disorders. These include systemic diseases, such as syphilis, amyloidosis, and lupus erythematosus, and the syndrome may occur following renal vein thrombosis, as a result of chemical toxicity (following bee stings or trimethadione [Tridione] therapy), and during the course of chronic glomerulonephritis which is preceded by a known attack of acute glomerulonephritis. All of these may be ruled out in the present case by the autopsy findings and the history. In addition, the nephrotic syndrome is thought by some to represent a distinct disease entity and by others to represent one stage in the course of chronic glomerulonephritis that is not preceded by a recognized episode of acute hemorrhagic nephritis. Histologic examination of nephrotic kidneys by the usual hematoxylin and eosin stains, showing primarily tubular changes, have led many to the latter belief. However, Ehrich and Forman [1] studied cases of lipoid nephrosis with the Ritter and Oleson polysaccharide stain and found that in some the only lesion was focal thickening and splitting of the basement membrane in most of the glomeruli, although some tufts appeared normal. Recent studies of kidney biopsy specimens by electron microscopy reported by Vernier et al.[27] have confirmed the different locus of pathologic change in nephrosis and glomerulonephritis.

Occurrence of the nephrotic syndrome in the neonatal period aids in distinguishing it from glomerulonephritis as a separate clinical entity, since acute glomerulonephritis as we know it is preceded by one to three weeks by a streptococcal infection. There was no evidence for such an infection, either prenatal or postnatal, in the case presented here, since cultures as well as serologic studies were negative for streptococcal infection in both the infant and the mother. In addition, it is known that albuminuria precedes the appearance of edema by several days or weeks in the nephrotic syndrome during a relapse; consequently, although gross edema was not observed until the 15th day of life, the onset of the disease undoubtedly was several days before then and possibly even prenatal.

Several references in the literature have been made to cases of so-called nephritis in the newborn period.[21-23] For the most part, they have not been documented with cultures, streptococcal antibody studies, or autopsy information. However, Kunstadter et al.[4] reported a case of the nephrotic syndrome in a premature boy of 1320 gm. whose edema appeared on the ninth day of life. Typical laboratory data were found. The infant died on the 71st day of life after a transfusion reaction. His nephrosis was not treated, nor had it remitted. Eiben et al.[5] reported a similar case in a boy weighing 2110 gm. who was noted to have edema on the fifth day and 3+ albuminuria on the eighth day of life. This child was treated with two courses of corticotropin (ACTH), one on the 31st day, with a total of 127 mg. over 9 days, and the other on the 70th day, with a total of 135 mg. over 11 days. There was some loss of edema and weight loss on both occasions, but there was no evidence of complete remission, since the albuminuria, hyperlipemia, and hypoproteinemia persisted. The child died of pneumonia on the 103d day of life.

Measurement of renal function by standard clearance techniques in the first few months of life reveal normal values to be approximately one-half of adult values when corrected for surface area. There is then gradual approach to adult levels over the first two years. Barnett et al.[6] found that normal infants had a GFR of 50 ml. per minute when corrected to 1.73 square meters (standard surface area). Rubin et al.[10] found GFR values of 46 to 73 ml. per minute corrected and ERPF values of 153 to 371 ml. per minute corrected in children under 3 months of age. Our initial determinations for GFR early in the disease in the present case were, then, within the normal range for the age, although the ERPF was somewhat elevated. This is consistent with the usual findings in nephrotic children during the acute phase.[2] In the second clearance measurement, 35 days later, there is a significant depression (40%) of the GFR, indicative of progressive renal changes.

Many workers feel that the proteinuria in the nephrotic syndrome is to a large extent related to increased glomerular permeability to serum proteins. If this is so, then proteins of larger molecular size would be expected to pass through the glomerulus with more difficulty than those of smaller size. Clearance measurements of proteins of different molecular size may therefore reveal the mechanism of changes in glomerular permeability. Lauson et al.[25] have demonstrated that protein clearance as related to GFR (C_{PR}/C_{IN}) expresses that minimum permeability of the glomerulus to protein per unit of water filtered, and it has been shown by McCrory[11] as well as by our laboratory[12] that this may be directly related to the extent of renal damage and hence to prognosis.

In addition, it is felt that the ratio of the clearance of proteins of larger molecular size, such as γ-globulin, to the clearance of albumin will vary directly with the extent of renal damage. The twofold increase (0.015 to 0.028) in the ratio of the clearances of albumin to inulin (C_{ALB}/C_{IN}), as well as the fourfold increase (0.002 to 0.008) in the ratio of the clearances of γ-globulin and inulin (C_{GG}/C_{IN}), is good evidence for an increase in the size of the defects in the glomerular membrane which permit proteins of larger molecular weight to escape more readily. Such an assumption is consistent with the downhill course of the patient.

The present patient was treated with two courses of steroids in large dosage without any evidence of complete remission. This same lack of response to steroids was seen in the case reported by Eiben. The experience over the past several years in this clinic with similar courses of steroid therapy (but in larger dosage for older persons) has resembled that of other clinics, namely, that diuresis together with clinical and laboratory remission occurs in about 80% of nephrotic children[13-15] if they are treated early in the course of the disease.

Cases in early life may contribute evidence as to the possible etiology of nephrosis. One prevalent theory of the etiology suggests that there is an autosensitization by the susceptible child to glomerular basement membrane protein, with progressive renal injury as antigen and antibody react locally. This theory is based on the work of Heymann [16] and Forman et al.,[24] who produced the typical nephrotic syndrome in the rat by injection of anti-rat-kidney rabbit serum. This nephrotoxic serum appears to be specific for capillary basement membrane, and a much more potent rabbit antiserum may be made by using glomerular basement membrane protein as antigen instead of whole kidney emulsion. This immunologic theory is supported by the work of Lange [17] and others, who found that serum titers of complement (thought to be incorporated or used up in the antigen-antibody reaction) are usually low during the acute phase of the disease and return to normal with recovery.

Good and others [18,19] have shown that although circulating γ-globulin occurs in higher concentration in newborn infants than in their mothers or in older children, the immune response of the newborn infant is probably deficient, since the newborn synthesizes little or no γ-globulin and circulating antibody for the first 6 to 12 weeks of life. If this be so, a mechanism in addition to or instead of the immunologic one may exist, at least in the neonatal nephrotic syndrome. The lack of response to steroid therapy may further indicate an etiology other than antigen-antibody union. In the present case the fall in serum γ-globulin levels is consistent with the normal decline in the first two to three months of life,[26] with superimposed loss in the urine, with marked proteinuria. The possibility that the nephrotic syndrome may occur only in the neonate who does produce antibody from birth cannot be excluded, however, since the decline of γ-globulin in the presented case may represent solely urinary loss. An alternate hypothesis is that the present case may be a result of antibodies to maternal or infant kidney antigen passively transferred from the mother. Against this, however, is the lack of maternal kidney disease and the failure of improvement of the patient with the natural decline of maternal antibodies in the first few months of life.

Attempts have been made to demonstrate renal antibodies in the sera of nephrotic children, but these have failed.[20] Future study must evaluate the place of cellular or fixed tissue antibody as well as congenital factors in this disease.

Summary and Conclusion

A case of the nephrotic syndrome in a neonatal premature infant is presented, with measurement of renal clearances during the course of the disease. A poor prognosis was predicted from the increase in the clearance of urinary protein in relation to the glomerular filtration rate as well as an increase in the clearance of protein of larger molecular size.

The present theories of the etiology of this disease are discussed. This case contributes evidence against several possible mechanisms of the etiology of the nephrotic syndrome in the newborn, including pneumococcal and streptococcal infections, poststreptococcal diseases, pyelonephritis, congenital anomalies, and renal vein thromboses. Furthermore, the concept of autogenous circulating antibody formation leading to progressive disease as a cause of nephrosis may not be applicable in the newborn in light of the data which indicate essentially an immunologic paralysis through the first several months of life.

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An Evaluation of the Immunohematological Tests Used in the Diagnosis of AB Hemolytic Disease

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Much has been written during the past decade concerning hemolytic disease of the newborn due to incompatibility between the Rh blood groups of the mother and her fetus. Criteria for the diagnosis of this type of erythroblastosis have been well established. More recently attention has focused on hemolytic disease due to incompatibility between the blood of the mother and her infant with regard to their ABO blood groups and the associated antibodies. In approximately 20% to 25% of pregnancies the ABO group of the mother and her fetus will differ. The majority of infants appear to be protected from harmful effects of this type of incompatibility. When AB hemolytic disease does occur, it is usually mild, and the majority of infants recover without transfusion. The severely jaundiced baby is in potential danger, however, and kernicterus may result.

Hemolytic disease due to anti-A and anti-B poses many problems in diagnosis. At this hospital all infants suffering from this disease have been Group A or Group B and their mothers have all belonged to Group O. Examination of the mother's blood for antibodies is complicated by the fact that anti-A and anti-B occur naturally in persons of Group O. The "hyperimmune" type of anti-A or anti-B, which can be detected in the maternal serum after the naturally occurring antibodies have been neutralized with AB polysaccharide, does not always reach a diagnostic level until the first week of the postpartum period. The direct Coombs test on the infant's cells is usually negative or, at the most, weakly positive.

Thus, the determination of abnormal antibodies in the mother's blood during pregnancy and a positive direct Coombs reaction of the red cells of an affected baby, which are the most valuable means for recognizing maternal Rh isoimmunization and subsequent hemolytic disease of the newborn, are of very limited value in the diagnosis of erythroblastosis due to anti-A or anti-B. Consequently, laboratory procedures which are not specific for the disease have been suggested in order to confirm this diagnosis. Spherocytosis and increased osmotic fragility, for instance, may be present in congenital hemolytic anemia. Reticulocyte counts greater than the normal 2% to 6% may be found in AB hemolytic disease, but reticulocytosis may also occur in the blood of infants suffering from Rh hemolytic disease or simple blood loss.

Since AB hemolytic disease is caused by maternal immunization to the fetal A or B antigens, immunohematological tests should theoretically be the ideal manner in which to confirm the diagnosis. The study to be reported was carried out so that an evaluation could be made of the various serological tests which can be readily employed in the routine diagnostic laboratory.

Methods

1. *ABO and Rh Blood Grouping.*—The antisera for these tests were obtained from the Ortho

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Pharmaceutical Corporation. The anti-D serum for slide test was used as a screening test to detect Rh-positive persons. In all cases, however, a more detailed Rh typing was done, with use of antisera for C, D, and E and, when necessary, for c and e. These were obtained from the Ortho Pharmaceutical Corporation and also from The Boston Blood Grouping Laboratory.

2. Screening Tests for the Detection of Rh Antibodies in the Maternal Serum.—The maternal sera were tested with a panel of trypsinized Group O red cells with the following Rh genotypes: CDe/CDe, cDE/cDE, and cde/cde. This proved an excellent screening test for the detection of Rh antibodies. The Rh-negative cell was also K+, Fy(a+), and indirect Coombs test was done with this cell to rule out immunization of the mother to anti-Kell or anti-Duffy.

3. Titration of Maternal Sera for Anti-A and Anti-B.—The method used was a modification of that proposed by Witebsky[1] for the titration of anti-A and anti-B after partial neutralization of the naturally-occurring antibodies. One part of maternal serum, two parts of AB-group-specific substance (Sharpe & Dohme), and one part of isotonic saline were placed in a small test tube. In a similar manner, a second tube containing one part of maternal serum, two parts of AB substance, and one part of Group AB serum was prepared. After an initial incubation of 20 minutes at room temperature, two serial dilutions were made from each of these solutions. A 5% suspension of Group A_1 and B cells, in isotonic saline for the first dilutions and in AB serum for the second dilutions, was added to the tubes. Titrations were allowed to incubate at 37 C for one hour. They were then centrifuged at 1000 rpm for one and one-half minutes and were read grossly and microscopically for agglutination.

The choice of the AB donor for the serum used as diluent in the titrations did not appear to be a major factor. Using the same serum containing hyperimmune anti-A and anti-B and the same A_1 and B cells, I have carried out titrations using as a diluent the sera from 20 different Group AB donors. All these titrations had identical endpoints.

The choice of the Group A_1 and B cells used in these titrations is of paramount importance. When the titrations are performed in the manner described above, only 85% of Group A_1 cells give good reactions. There appears to be a slight variation in the reactivity of Group B cells also. The reason for this is obscure at the present time, but further investigations are in progress. From a practical point of view, however, when neutralized anti-A and anti-B titrations are being done for the diagnosis of AB hemolytic disease, it is essential to choose Group A_1 and B cells which are strongly reactive. The best way to ensure this is to test all cells before they are used, with a neutralized serum known to contain hyperimmune anti-A or anti-B.

Performing titrations by the indirect Coombs test instead of using AB serum is not only more laborious but gives no extra information. Titers obtained by the indirect Coombs test of 23 maternal sera were approximately the same as those obtained when AB serum was used as the diluent. The only advantage of the indirect Coombs titration is that rouleaux formation is eliminated. This may be troublesome when AB serum is used, especially if incubation at 37 C is prolonged.

4. The *Direct Coombs Test.*—The Coombs reagent used in this test was obtained from the Ortho Pharmaceutical Corporation. It is primarily prepared for the investigation of infants with Rh hemolytic disease. The test was performed by using a 2% suspension of the infant's red cells after they had been washed four times in isotonic saline. To this suspension an equal volume of Coombs reagent was added, and after centrifugation at 1000 rpm for one and one-half minutes it was read for agglutination both grossly and with the low power of the microscope.

5. *The Indirect Coombs Test.*—This was done by incubating two drops of the infant's serum with two drops of a 5% saline suspension of Group A_1 or B cells for one hour at 37 C. A Coombs test was performed on these cells after they had been washed three times in isotonic saline. Since this test was used to demonstrate anti-A or anti-B in the infant's serum, an A_1 cell was used if the baby was Group A and a Group B cell if the infant was Group B. The A_1 and B cells used were known to react with hyperimmune anti-A and anti-B (see above).

6. *Löw's Papain Test.*—Recently Löw[2] described how papain activated with cystein could be used for the detection of incomplete Rh antibodies. In this study this substance was used in the detection of anti-A or anti-B in the infant's serum. One drop of the infant's serum and one drop of Löw's papain preparation were incubated at 37 C for 10 to 15 minutes with one drop of a 2%-5% saline suspension of Group A_1 or B cells, depending on the group of the child. After centrifugation at 1000 rpm for one minute, this was read grossly for agglutination.

7. *The Witebsky "Drop" Test.*[3]—The baby's cells were suspended on a slide over an illuminated viewing box in three different diluents: (*a*) in a drop consisting of one part of normal adult serum to two parts of 30% bovine albumin; (*b*) in a drop of normal adult AB serum; and (*c*) in a drop of saline. These slides were gently rocked, and the presence or absence of agglutination within three minutes was noted by gross inspection.

When doing this test it is essential that a heavy suspension of cells be used. This can conveniently be taken from the clot by means of a wooden applicator.

Case Material

Blood from two groups of mothers and their infants were studied.

I. Clinically Affected Group.—Investigations were carried out on 100 infants (and their mothers) who became jaundiced during the first day of life and were admitted to The Hospital for Sick Children. Rh and other types of hemolytic disease, primary liver disease, or infection was carefully excluded as the cause of jaundice. Since these babies were not all admitted immediately after birth, they were arbitrarily divided into three groups, depending on the time at which the laboratory tests were done, i. e., from birth to 24 hours, 24 to 48 hours, and over 48 hours of age. In all cases the mother was Group O. Eighty-three infants were Group A, and seventeen were Group B.

II. Control Group.—This consisted of 115 Group O mothers who had 90 Group A and 25 Group B infants. Clinically all these children remained healthy and did not become jaundiced. Blood was obtained from the mother on the first day post partum, and cord blood was taken from all the infants. These specimens were obtained through the cooperation of Dr. Alice Gray, of Women's College Hospital, Toronto.

Investigation of Blood from the Mother

The ABO blood group and Rh type of all the mothers was determined. In addition, the serum of the mother was screened for the presence of Rh antibodies, anti-Kell, and anti-Duffy. Titration of the hyperimmune anti-A and anti-B after partial neutralization of the serum with AB polysaccharide was done routinely.

TABLE 1.—*Titration of Maternal Sera for Anti-A and Anti-B After Partial Neutralization with AB Polysaccharide*

Time of Testing	No.	Titer up to 1:64	Titer 1:256 or Over	% Significant
Clinically affected group				
Delivery–24 hr. post partum	42	20	22	52.5
24–48 hr. after post partum	44	11	33	
Over 48 hr. after post partum	14	0	14	100
Control group				
Delivery–24 hr. post partum	115	110	5	4.5

Results

Titration of Maternal Sera for Hyperimmune Antibodies.—In the control group many mothers showed hyperimmune anti-A and anti-B in low titer. It can be seen from Table 1 that in this group 95.5% of the mothers had hyperimmune antibodies of titers of 1:64 or less. The highest titer encountered was 1:256, and the remaining 4.5% of mothers fell in this category.

In mothers who had babies with AB hemolytic disease, however (the clinically affected group), 52.5% had hyperimmune antibodies of a titer of 1:256 or over when the tests were done on the first day post partum. The number reaching the titer of 1:256 or greater on the second day post partum was 75%, and after 48 hours post partum this figure rose to 100%.

There is a decisive difference in the hyperimmune antibody level between mothers in the control group and those with clinically affected infants at the titer 1:256. A separate study has been in progress at this laboratory [4] designed to investigate further the development of hyperimmune anti-A and anti-B following vaccination for typhoids, paratyphoid A, paratyphoid B, tetanus, and diphtheria (TABTD vaccination). At the present time, a total of 570 specimens of blood taken from members of the Canadian Armed Forces, routine blood donors at The Hospital for Sick Children, and members of the hospital staff have been examined for the presence of anti-A and anti-B. The methods used included the titration of these sera after partial neutralization of the antibodies with AB polysaccharide. Only three of these specimens, when tested by this method, have shown a titer higher than 1:256, and the proportion showing titers greater than 1:64 compares favorably with that in the control group of mothers in the series reported. Since levels of hyperimmune antibodies greater than the titer of 1:256 were frequently encountered in mothers whose infants had AB hemolytic disease, it was assumed that AB heterospecific pregnancy was in itself a cause of

maternal anti-A or anti-B immunization. The immunizing substance is probably the A or B antigen of the fetus.

Further Titrations for Hyperimmune Antibodies During the First Week Post Partum.—1. Mothers with Normal Infants: Twenty mothers in the control group whose hyperimmune antibodies had titers of 1:64 or less were retested on the fifth to seventh day post partum. There was occasionally a rise in titer of one tube, but none rose to 1:256 or over. The five mothers in this group who had hyperimmune antibodies to a titer of 1:256 on the first day post partum showed exactly the same titer at seven days post partum.

2. Mothers of Infants with AB Hemolytic Disease: Twenty-four mothers in this group whose hyperimmune antibodies were below the titer of 1:256 when tested on the first or second day post partum were retested before they left hospital, usually about the sixth or seventh day after the baby was born. In each instance the hyperimmune antibody titer had risen to at least 1:256, and many surpassed this figure. The fact that the titer of hyperimmune antibodies rises during the first week post partum in these mothers, I feel, is very significant and certainly deserves further study.

Fate of the Hyperimmune Antibodies.—The rate of disappearance of the maternal hyperimmune maternal antibodies was more difficult to determine. They appear to reach their peak during the first 10 days post partum and then remain steady for the next four to six weeks. After that the majority diminish slowly in titer, but there is a large individual variation.

Should another pregnancy intervene, the antibodies quickly return to a high level. This high titer cannot be used to prognosticate the occurrence of a second infant with AB hemolytic disease. Seven women who had babies with AB hemolytic disease were investigated during their next pregnancy. All of these mothers had high titers of hyperimmune antibodies, which remained steady throughout the second pregnancy. In two cases the babies were Group O and unaffected, and the remaining five babies were Group A. The Group A infants suffered from hemolytic disease, but, surprisingly, it was not as severe as in their previous siblings.

Hemolysin Tests.—Presence of hemolysins to Group A or B cells, in sera containing hyperimmune anti-A or anti-B, was described by Mollison.[5] This test, however, has little practical application in the diagnosis of AB hemolytic disease. We found, as did Zuelzer,[6] that the hemolysin test was too sensitive. Whereas it is true that the sera of mothers who have affected babies contain hemolysins, many mothers in the control group who had low titer anti-A or anti-B had hemolysins to A_1 or B cells. There did not appear to be a strict correlation between the hyperimmune antibody titer and the strength of the hemolysin.

Investigations of the Bloods from the Infants

The ABO and Rh group, with Rh subtyping, was determined on all infants. The other tests done on the blood from the infant will be described separately.

1. *The Direct Coombs Test.*—This was performed on the blood from all the infants. Only 39% of infants in the clinically affected group, when tested during the first 24 hours, showed positive results (Table 2). When the infants were tested after 24 hours of age, the number of positive results was even less. In no instance was the Coombs test found to be strongly positive. Red cells of infants in the control group showed uniformly negative direct Coombs reactions.

TABLE 2.—*Direct Coombs Test on Infants' Blood*

Time of Testing	No.	Weak Positive	Negative	% Positive
Affected infants Birth–24 hr.	42	16	26	39
24–48 hr.	44	9	35	20.5
After 48 hr.	14	2	12	14
Control group Cord blood	115	0	115	0

TABLE 3.—*Indirect Coombs Test on Infants' Sera with Adult A_1 or B Cells*

Time of Testing	No.	Positive	Negative	% Positive
Affected Infants Birth–24 hr.	42	39	3	93
24–48 hr.	44	32	12	73
After 48 hr.	14	8	6	58
Control group Cord blood	115	0	115	0

2. *The Indirect Coombs Test.*—In the control group anti-A or anti-B could not be demonstrated in the infant's serum even though many of the mothers had low titer hyperimmune antibodies, as described previously (Table 3). In the clinically affected group, however, anti-A or anti-B was demonstrated by the indirect Coombs test in 93% of infants tested during the first day of life. It should be noted that it was in the Group A infants that the anti-A was demonstrated and, similarly, the anti-B in the Group B infants. After the first 24 hours the test becomes of less value, since fewer positive results were found. Presumably this is due to a neutralization of the anti-A or anti-B by the A or B substance in the infant's tissues.

3. *Löw's Papain Test.*—The cord serum of 25 infants in the control group was tested by this method, and there were uniformly negative results (Table 4). In the clinically affected group the serum of 17 infants tested on the first day of life contained anti-A or anti-B when Löw's papain test was used, and only 2 infants gave negative results when tested between 24 and 48 hours of age. Three positive reactions were obtained with papain when the indirect Coombs test was negative, suggesting that Löw's papain may be more sensitive in demonstrating traces of anti-A or anti-B in these infants' sera.

4. *The Witebsky "Drop" Test.*—The "drop" test of Witebsky was done on all children of the control group, with negative results. The positive reactions obtained when 66 of the clinically affected infants were tested paralleled the results obtained by the indirect Coombs test (Table 5). I found, like Witebsky,[3] that agglutination was observed with the blood of infants suffering from AB hemolytic disease when Group AB serum was used as diluent. Although this test has the advantage of simplicity and speed, one has to be careful in the interpretation of the result in some cases, since rouleaux formation can simulate weak agglutination.

Summary of the Results

1. *Tests on the Maternal Serum.*—Hyperimmune anti-A and anti-B antibodies may be present in the maternal serum in low titer in Group O mothers who have normal Group A or B babies. In about 50% of Group O mothers whose infants have AB hemolytic disease, the hyperimmune antibodies are within the "normal" range on the first day post partum, but if they are retested at the end of the first week post partum a rise in titer will be noted. The level taken to indicate isoimmunization of the mother to the A or B factors of the infant was 1:256.

2. *Tests on the Infant.*—These are only reliable if done during the first, and possibly the second, day of life. Löw's papain

TABLE 4.—*Use of Löw's Papain Test to Demonstrate Anti-A or Anti-B in the Infants' Sera*

Time of Testing	No.	Positive	Negative	% Positive
Affected Infants Birth–24 hr.	17	17	0	100
24–48 hr.	20	18	2	90
After 48 hr.	3	0	3	0
Control group Cord blood	25	0	25	0

TABLE 5.—*The Witebsky "Nine Drop Test"*

Time of Testing	No.	Positive	Negative	% Positive
Affected Infants Birth–24 hr.	27	24	3	89
24–48 hr.	27	19	8	70
After 48 hr.	12	3	9	25
Control group Cord blood	115	0	115	0

test, the indirect Coombs test with adult A_1 or B cells and the child's serum, and the Witebsky "drop" test give a high percentage of positive results during this time. The direct Coombs test is of little value as a positive diagnostic aid.

Comment

One of the interesting features which emerged from this study was the inability to detect anti-A or anti-B by the indirect Coombs test in the cord blood of infants in the control group, whereas it was demonstrated frequently in clinically affected babies. Thus, from these results we can conclude that proof of anti-A or anti-B in the serum of infants suspected of AB hemolytic disease is strong presumptive evidence that their red cells have been damaged by this antibody. The above results do not entirely agree with the observations of Jacobowicz and Bryce,[7] Wiener,[8] and Zuelzer,[9] who found homologous antibodies in apparently normal Group A or B infants on a few occasions. Zuelzer, however, concluded that a positive indirect Coombs test with an adult A_1 or B cell, depending on whether the baby is Group A or B, respectively, was a good screening test for AB hemolytic disease. He did not stress, however, the time factor involved. In the study described the indirect Coombs test was most valuable when done on the first day of the baby's life. After that time it becomes variable and is therefore less reliable.

Use of Löw's papain test to demonstrate anti-A or anti-B in the sera of infants with AB hemolytic disease showed very promising results. Admittedly, the number of affected and normal infants in which this test was used was small, but decisive results were obtained. These early results suggest that it may be even more sensitive than the indirect Coombs test, and it is certainly easier to carry out.

When examined as a whole, the hyperimmune antibody patterns in the mothers of the control group and in the clinically affected group showed striking differences. But in the individual case, especially when the titrations are carried out on the first day post partum, the maternal hyperimmune antibody level may be within the limits found in "normal" mothers. There is, however, a different antibody pattern in the two groups during the first week post partum. In Group O mothers with normal Group A or B babies the anti-A and anti-B titers after neutralization showed little change. Twenty-four of the mothers in the clinically affected group who showed hyperimmune antibodies in the "normal" range on the first or second day post partum had a significant rise in titer of the hyperimmune antibodies, to a level of at least 1:256, by the end of the first week post partum.

Zuelzer [3] found a small but definite rise in saline anti-A and anti-B and the development of low-titer hyperimmune antibodies in the post partum period in a number of Group O mothers with normal A or B babies. His subsequent testing of the mother's sera was not done, however, until three weeks post partum. He correlated this rise with the secretor status of the infants. Antibody titrations were not done on the normal group in our study after the first week post partum, since this appeared to give a clear-cut difference on the antibody patterns in the control and clinically affected groups. No attempts were made to carry out secretor tests in the infants. Despite this omission, it is permissible to conclude from the studies reported that there is a correlation between the rise of hyperimmune antibodies in a Group O mother, during the first week post partum, and the birth to her of a Group A or B infant suffering from AB hemolytic disease.

In the majority of cases of infants with AB hemolytic disease the diagnosis can be confirmed by serological tests alone. It can be seen that the tests on the infant's blood show better results when these are done early. Since affected infants become jaundiced during the first day of life, it is important that investigations be commenced immediately. The indirect Coombs test,

Löw's papain test, and the Witebsky "drop" test will give a high percentage of positive results. It is true that on the first day post partum the mother's hyperimmune antibodies may not be at a significant level, but this should not detract from the diagnosis in face of other evidence, when her serum is examined at this time.

If, on the other hand, the infant is not seen until after 48 hours of age, the indirect Coombs test and the papain test on the child's serum may well be negative and will be of little value in confirming the diagnosis of AB hemolytic disease. By this time, however, the titer of hyperimmune anti-A or anti-B in the mother's serum will have reached a significantly high level, permitting confirmation of the diagnosis.

The direct Coombs test, even though many infants show negative reactions, should be done in every case which is suspected to be AB hemolytic disease. An unexpected strongly positive Coombs reaction serves as a warning that erythroblastosis is present, due to causes other than ABO blood group incompatibility. Careful investigations should be carried out to exclude the more uncommon types of Rh isoimmunization or involvement of other blood group systems.

Summary

Investigations have been carried out on 115 Group O mothers and their normal Group A and B infants and on 100 Group A and B infants (and their mothers) admitted to The Hospital for Sick Children suffering from AB hemolytic disease.

From these investigations the value of the various immunohematological tests can be assessed. The most valuable tests during the first 48 hours of the child's life are usually tests done on the infant's blood. For instance, the indirect Coombs test and Löw's papain test, used for the detection of anti-A and anti-B in the sera of Group A and Group B babies, respectively, and the Witebsky "drop" test show a large percentage of positive results. After 48 hours these tests are unreliable. The direct Coombs test is of little value as a positive diagnostic aid. During the first 48 hours of life investigation of the maternal serum for hyperimmune anti-A or anti-B may be of little value, since the titers obtained may fall within the "normal" range. After 48 hours, however, significantly high titers should be obtained when the baby is affected with AB hemolytic disease. This is helpful, since by this time negative results are usually obtained on examination of the infant's blood, and so the high hyperimmune antibody titer of the mother can be used to confirm the diagnosis of AB hemolytic disease in the infant.

Miss Isabel Scott and the technical staff of the Rh laboratory performed many of the laboratory procedures in this study.

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Chromosomal Sex Test

Applications in Pediatrics

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The description by Barr and Bertram[1] of a sex-related morphologic difference in the nuclei of neuronal cells of the cat central nervous system has led to the development of a new diagnostic tool in the study of certain pediatric endocrine disorders. A nuclear morphologic difference between the sexes has been reported for the cat, dog, mink, marten, ferret, skunk, raccoon, goat, deer, monkey,[2,3] and man.[2-6] The test as originally devised for application to human subjects utilized a skin biopsy specimen.[5,7,8] It has been modified to use cells from such actively growing areas as the oral mucosa,[6,9,10] vaginal mucosa,[11] and amniotic membranes.[12,13] The chromosomal sex test has been applied to patients with gonadal dysgenesis,[6,8,9,14,15] female pseudohermaphroditism,[3,5,7,6,15] male pseudohermaphroditism,[14,18] true hermaphroditism,[15,18] and Klinefelter's syndrome.[19-21]

The present report illustrates the usefulness and limitations of this technique in clinical pediatrics.

Materials and Methods

The observations were made on persons attending the endocrine clinic of The Children's Orthopedic Hospital, Seattle.

The chromosomal sex test was performed according to the technique of Moore and Barr.[10] The oral mucosa was scraped with a flat metal spatula, and this material was puddled on a glass slide surfaced with Mayer's albumin. The slide was immersed immediately in either modified Davidson's fixative[8] or Papanicolaou's fixative (equal parts by volume of ether and 95% ethyl alcohol). After fixation the slides were stained by the Feulgen technique for deoxyribonucleic acid in the chromosome[9] or with cresyl violet. Papanicolaou's stain demonstrates chromosomal sex material in vaginal[11] and oral smears.[6]

A microscopic search was made under oil immersion for the characteristic hyperchromatic mass of stained chromatin with planoconvex form lying against the nuclear membrane.[10] When this could be demonstrated in 12% or more of suitable cells, the smear was read as "chromatin-positive." False "chromatin-negative" results may be obtained if the nucleoplasm is not well preserved.

Dr. Murray Barr personally reviewed our smears.

The height and weight percentile charts referred to are those compiled from the data of Harold Stuart and associates.[24,25]

Report of Cases

CASE 1.—*Bonnevie-Ullrich Syndrome with Gonadal Dysgenesis*[15,21]

A 5-month-old infant was referred by Dr. Robert Hoffman because of congenital lymphedema, webbing of the neck, and unusual facies. The diagnosis of gonadal dysgenesis was based on the oral smear.

The family history was noncontributory. The mother was 23 years of age, and this was her first pregnancy. The pregnancy was uneventful except for two upper respiratory diseases during the first trimester. An analysis of the mother's diet during pregnancy revealed an average caloric content of 1600. The daily intake of Fe (9.1 mg.), thiamine (1.1 mg.), and nicotinic acid (10 mg.) were less than the recommended daily allowances but not unusual. Approximately one alcoholic beverage and two packages of cigarettes were consumed daily. The birth was at term, and the weight was 2710 gm. The infant developed a breast abscess which was surgically drained during the first week of life. The presence of neonatal breast hypertrophy was not recalled by the parents.

Some of the major points of note on physical examination can be seen in Figure 1. The child's

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Fig. 1 (Case 1).—Patient at 5 months of age. Gonadal dysgenesis with Bonnevie-Ullrich syndrome, illustrating the neck and ear deformities and demonstrating in addition the lowered posterior hair line and lymphedema of the dorsum of the hand.

Data in Cases 1 and 2

Case	Age	Ht., Cm.	Ht. Age*	Bone Age, Yr.	Wt., Kg.	Span, Cm.	Lower Segment†	Head, Cm.	Chest, Cm.	Abd., Cm.
1	5 mo.	63.9	5 mos.		6.4	58.4	39.5%	41	38	36.9
2	5 yr.	88.0	2 2/12 yr.	3 1/2	13.8	88.0	48.0%	54	57	51.0

* The height age was obtained from the data of Stuart.[14,15] His value for the 50th percentile was used as "normal."
† The distance from the upper aspect of the symphysis pubis to the floor was expressed as per cent of the total height. The 50th percentiles for females are as follows: birth, 38.5%; 12 mo. 41.2%; 6 yr. 47.8%; adult, 51.5%, as calculated from Simmons.[16]

height was average for a 5-month-old, and other measurements are recorded in the Table. The blood pressure by the flush method was 120 mm. Hg in the hand but only 70 mm. in the foot. The femoral pulses were strong. The head was of normal shape, but the ears were elongated caudally and folded over. There was marked redundancy of the lateral cervical skin folds, but, owing to the relative shortness of the neck at this age, the fold did not resemble a "web" unless drawn out by an examiner. There were also moderate-sized medial epicanthal folds. There was pitting edema of the feet and hands. The subcutaneous tissues elsewhere were slightly redundant but of normal elasticity. The nipples were not seen, and in their place were small dimples. The areolae measured 0.7 cm. in diameter and seemed more widely spaced than normal (internipple distance, 10.8 cm.; transthoracic diameter at nipples, 15.0 cm.). The spleen was slightly enlarged. The carrying angle of the forearms was normal, but the posterior cervical hairline extended lower than usual. The clitoris was approximately 0.7 cm. in length; the external genitalia were those of a normal immature girl.

A smear of the oral mucosa was stained as described and was "chromatin-negative," resembling that ordinarily seen in the male.

At the age of 16 months the height was 76.5 cm., indicating a decrease from the 50th to the 25th height percentile. The flush blood pressure was 90 mm. of Hg in the hand and 70 mm. of Hg in the foot. Mental development had been normal.

CASE 2.—*Gonadal Dysgenesis with Only Stunted Growth*

A 5-year-old girl was referred because of stunted physical growth. Although the configuration of her chest was unusual, the only indication of gonadal dysgenesis was a male type of chromatin configuration.

The prepartum period was thought to have been normal. The birth weight was 2960 gm. At 2 months of age she began having spells of unconsciousness associated with stiffening and cyanosis. These episodes were never associated with fasting and gradually decreased at about the age of 3 years. An insulin-tolerance test and several fasting blood sugar determinations were normal at 2½ years of age. Although her protein-bound iodine was 7.5γ per 100 ml. of serum and she had had no signs of hypothyroidism, a trial on 1 grain (65 mg.) of dessicated thyroid was carried out for 18 months. There was no clinical improvement, and the linear growth continued at an unchanged rate. She had had no polyuria, eye symptoms, or headache suggestive of pituitary envolvement. Her mental development had progressed normally. The previous heights and weights plotted on a growth chart showed a steady increase, but the curves were considerably below the third percentile.

Fig. 2 (Case 2).—Patient with gonadal dysgenesis, illustrating habitus and the "shield-like" chest.

When examined at 5 years of age, she was an active intelligent child whose height was that of an average 2-year-old (Fig. 2). Her measurements are recorded in the Table. The head was prominent in the frontal region. Her proportions as judged by naso-orbital configuration, span, and lower segment were close to those of a 5-year-old. These normal proportions in a child with marked reduction in height age were slightly suggestive of achondroplastic dwarfism. The blood pressure was normal, and the femoral pulses, strong.

The nipples appeared widely spaced (internipple distance, 13.5 cm.; transthoracic diameter at the nipples, 26.5 cm.). The thorax was wider than normal. The nipples measured 0.2 cm. and the areolae 0.9 cm. in diameter. There was no webbing of the neck or definite peripheral edema. The dorsum of the phalanges appeared puffy, owing to a characteristic tightening of skin at the interphalangeal joints. The posterior hair line and carrying angle of the arms were normal.

The osseous developmental age was approximately 3½ years. No osteoporosis was detected. The following pertinent secondary epiphyseal centers were present at five years: capitulum humeri, tuberculum majus humeri, trochanter major, and all phalangeal and metacarpal centers. The triquetrum, head of fibula, and unciform bone were absent. The serum Ca, P, cholesterol, fasting blood sugar, and protein-bound iodine were normal, as was a routine urinalysis. The skull x-ray was negative.

An oral smear was "chromatin-negative," resembling the male type of pattern.

CASE 3.—*Female Pseudohermaphroditism Due to Congenital Adrenal Hyperplasia*

A 9-week-old white infant presented with ambiguous external genitalia and in a shock-like state. Urinary 17-ketosteroid determinations were not obtainable, owing to anuria, but the female chromatin pattern helped to confirm the diagnosis.

The prepartum and birth were normal. The birthweight was 2600 gm. Although the genitalia were noted to be ambiguous at birth, the child was given a male name. After the first two weeks the infant began to drink his proprietary formula poorly and subsequently failed to gain weight and seemed to be weak. The skin had seemed more darkly pigmented than normal. Vomiting and diarrhea were not significant, although one large black stool occurred shortly before admission to another hospital. While at another hospital, the infant continued to do poorly and in spite of numerous clyses failed to gain weight or become hydrated. Consequently, a transfer to The Children's Orthopedic Hospital was made.

At the time of admission, the weight was 3000 gm. The patient appeared seriously ill. His temperature was (93.7 F) (34.3 C) by rectum, and B. P. was 15 mm. Hg by the flush technique at the hand. The length was 56 cm., and the head circumference, 34.5 cm. The proportions appeared to be normal, but they were not measured because of the patient's condition. All the signs of extracellular fluid loss (poor turgor of the skin, depressed fontanelle, sunken eyes) were present and, in addition, the skin was more pigmented than usual, particularly in the areas of areolae and genitalia. The phallus was bound down ventrally by a chordee and measured about 2.5 cm. in length and 1.2 cm. in width. At the base of the phallus there was an orifice. The labia majora were pigmented and wrinkled. Rudimentary labia-minora-like projections extended from the midperineal area to about one-half way up the phallus. There was no acne, pubic hair, or increase in muscle size. The abdomen was slightly distended and silent. The examination of the chest revealed no abnormalities.

Laboratory work revealed a Hb. value of 14.7 gm. per 100 cc. and a normal white blood cell count. The differential count showed 74% polymorphonuclear leukocytes, 18% lymphocytes, 6% monocytes, and 2% eosinophils. In spite of the severity of the illness eosinophils were still present. The initial serum potassium was 6.5 mEq. per liter,

and the sodium, 118 mEq. per liter. The blood urea nitrogen was 98 mg. per 100 cc.

A flat plate of the abdomen revealed gas in the biliary tree. Injection of radiopaque material into the urogenital sinus failed to outline a vagina. The oral mucosal smear was "chromatin-positive," resembling the female pattern.

The patient remained anuric and in shock in spite of intensive therapy, which included blood transfusions, a total of 95 mEq. of Na in the first 24 hours, desoxycorticosterone acetate (3 mg.), cortisone, antibiotics, and other general supportive measures. In spite of this rather large intake of sodium in this anuric patient, only slight edema developed. Death occurred 48 hours after admission.

Autopsy Findings: The pertinent findings at necropsy revealed the phallus of the external genitalia to be a hypertrophied clitoris, at the base of which was an orifice admitting a probe which readily entered the urinary bladder. Within the pelvis was an infantile uterus 2 cm. in length, with Fallopian tubes and ovaries. No gonads of a testicular nature were found. A small rudimentary vagina was present, the proximal end of which surrounded the cervix in normal fashion but the distal extremity of which was transversed by an atretic membrane, approximately at the level of the vesicourethral orifice. The patent urethra extended for a distance of 3 cm. from this point through the perineal tissues to its exit at the base of the phallus.

The adrenal glands were enlarged bilaterally and presented the peculiar grayish-green color which we have noted to be a fairly constant finding in cases of congenital adrenal hyperplasia. Both organs were firm to palpation, weighing an aggregate 12 gm. and presenting on section a marked increase in thickness, though retaining the normal architectural arrangement of cortex and medulla. Microscopic examination revealed hyperplasia of cortical tissue in the zona reticularis but no evidence of nodular tumor formation.

Sections of ovaries were histologically normal for this age, with numerous primordial follicles present.

Except for evidence of peritonitis and bronchopneumonia, the remainder of the autopsy findings were not particularly noteworthy.

Comment

Method.—In our experience, we have found the Feulgen stain to be technically the most difficult and hazardous in that occasionally chromatin masses did not stain adequately for correct reading of the slide. The cresyl violet was found to vary in suitability among manufacturers. The Coleman and Bell product was most satisfactory. This dye does stain bacteria, and these need to be differentiated in reading the slides. Although the Papanicolaou stain was not used for the cases discussed, recent experience seems to indicate that this may be the most satisfactory for general use. It is readily available in prepared form and does not stain bacteria as heavily as does cresyl violet, while the sex chromatin shows up well.

Gonadal Dysgenesis.—Grumbach, Van Wyk, and Wilkins[14] advocated the term gonadal dysgenesis for cases which had previously been called "Turner's syndrome," "ovarian agenesis," "primary ovarian insufficiency with decreased stature," and "syndrome of rudimentary ovaries" and "Bonnevie-Ullrich syndrome." The common finding in these syndromes is failure of gonadal development. Jost[38] and Wilkins[36] independently predicted in 1950 that half of these patients would be genetic males, if a test of genetic sex should be developed. This prediction arose from the work of Jost[26] with rabbits and Raynaud and Frilley with mice,[27] in which early removal or destruction of the fetal gonads invariably resulted in female development of the genitalia. The application of the chromosomal sex test, as developed by Barr and associates, has verified the occurrence of male chromatin pattern in some of these persons. An unsual predominance of the male pattern has not been explained. The presence of male pattern tends to substantiate the concept that injury of as yet unknown nature to the embryo results in castration and that in the case of the male this is followed by sexual differentiation along female lines. Therefore, as previously pointed out by Grumbach et al.,[14] gonadal dysgenesis with the male type of nuclear chromatin is actually an example of the most complete form of male pseudohermaphroditism.

The chromosomal sex test is very nearly specific in this syndrome. The only other conditions which give a male chromatin pattern in patients with female genitalia are

two rare syndromes: true hermaphroditism and a special type of male pseudohermaphroditism, the feminizing testicular syndrome. Shortness of stature is not associated with either of these. Associated congenital anomalies also do not occur with the same frequency. Although a specific pathological diagnosis was not made in the two reported cases, previously explored patients[8,14,37] have indicated the specificity of this test under these circumstances.

Since associated anomalies may vary greatly in severity and incidence, the syndrome may not be suspected until the age of puberty, when failure of estrogenization with some sexual hair and usually elevated urinary follicle-stimulating hormone occurs. However, certain congenital anomalies may warrant application of the test prior to puberty. Jackson,[28] Turner,[29] Grumbach,[14] and Oberman[30] have discussed these abnormalities. The most consistant finding is short stature. This may be noted usually by the end of the first year of life. The Bonnevie-Ullrich syndrome of webbing of the neck and congenital lymphedema is commonly associated with gonadal dysgenesis. Another characteristic finding is the "shield-like" chest with pin-point nipples spaced far apart on a broad, stocky thorax. Mental retardation has been reported in a few of these children. Coarctation of the aorta or unexplained hypertension in a short girl should indicate the need to consider gonadal dysgenesis. The diagnosis should be considered in female infants born with multiple congenital abnormalities.

An early diagnosis based on finding chromatin-negative smears allows accurate prognosis of ultimate height (usually between 50 and 58 in.) and sterility. Exploratory laparotomy is less frequently necessary, and the use of various endocrine preparations before the time of onset of puberty is prevented. Later, a rational program of estrogen substitution therapy can be instituted. These measures improve the care of the patient.

Female Pseudohermaphroditism Secondary to Congenital Adrenal Hyperplasia.—Congenital adrenal hyperplasia may result in varying degrees of masculinization of the female.[31] These persons have normal ovaries and internal genitalia but varying degrees of clitoral hypertrophy and fusion of the labia majora. An extreme case, in which there was an apparently normal penis and scrotum with undescended gonads, has been reported.[32] The more usual presenting picture in the female is of a newborn infant with ambiguous external genitalia. If the salt-losing aspect of the syndrome is present, the diagnosis may be suspected earlier and established by appropriate hormonal assays on the urine. However, there may be no other evident disorder noted until later in childhood, at which time accelerated growth, bony maturation, and evidences of virilization occur. Because of this lack of early clinical evidence of the syndrome, other than ambiguous genitalia, we feel that such children should have the chromosomal sex test, in addition to urinary 17-ketosteroid determination, to aid in planning treatment. A female chromatin pattern is only presumptive evidence of this syndrome. The only other conditions in which this might be present would be true hermaphroditism and the rare instance of female pseudohermaphroditism due to some cause other than congenital adrenal hyperplasia, such as produced by arrhenoblastoma in the mother during pregnancy.[31] A high level of 17-ketosteroids or pregnanediol in the urine is still the most important laboratory test for establishing the diagnosis of congenital adrenal hyperplasia. The test for chromosomal sex becomes of greatest clinical value in this syndrome when urine hormone studies are not available, as in the anuric patient cited above.

Other Clinical Conditions.—In the true hermaphrodite either male or female chromatin pattern may be observed, although the female type predominates.[15,18] A gynandromorphic condition in which one side of the body is chromatin-positive and the other side is chromatin-negative has not been reported.

The feminizing testicular syndrome [31,33,36] is a familial condition in which testes are located in the inguinal canals or abdomen and the external genitalia are those of a normal female. These estrogen-producing testes presumably cause the fetal external genitalia to differentiate along female lines, and at pubescence they can cause the appearance of normal estrogenic manifestations. The presence of bilateral inguinal hernias or masses in a girl should be an indication for determining the genetic sex. This serves to give a presurgical estimate of the type of gonad present and allow consideration of proper long-term planning.

The observation that a "chromatin-positive" smear may be obtained in Klinefelter's syndrome [19-21] suggests that this may be a method for detecting such cases before puberty. Valuable information as to pathogenesis might thus be obtained.

We wish to emphasize that the findings of the nuclear chromatin test are of little help in actual assignment of the gender of future rearing. For a full discussion of factors to be considered in assignment of sex, reference should be made to Wilkins et al.[31] and Money et al.[34]

Summary

The technique of the chromosomal sex test with use of oral scrapings is described.

Practical applications of the test in diagnosis of the following pediatric conditions are discussed: (*a*) gonadal dysgenesis, (*b*) female pseudohermaphroditism, (*c*) male pseudohermaphroditism, (*d*) true hermaphroditism, (*e*) Klinefelter's syndrome.

Two examples of gonadal dysgenesis are presented, one in which there was an associated Bonnevie-Ullrich syndrome and one in which there was only stunted growth and a shield-like chest. Clinical and autopsy findings in a case of female pseudohermaphroditism due to adrenal hyperplasia are presented.

Dr. Murray Barr aided in standardizing the method. Mrs. Ardella Bennett gave technical laboratory assistance. Drs. Robert Aldrich, Fred Moll, and Bradford Ostrom gave valuable assistance by criticizing the manuscript. Dr. Mary Lou Johnson obtained the nutritional history in Case 1.

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Relationships of Cerebral Disorder to Faults in Dental Enamel

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The origins of cerebral disorders in children are often difficult to discover. Causes of brain damage may be suspected, but the lack of confirmatory evidence leaves doubt that a suspected cause was, in fact, responsible for the abnormalities observed. To have a way of confirming suspected causes of early brain damage would be a great advantage. The thought occurred to us that some of the abnormal processes causing damage to the brain might also produce defects in the enamel forming on the teeth at the time. Since the chronological pattern of enamel growth has been established,[1] the amount of enamel formed at a given age being known, it should be possible to tell when a disturbance had occurred which caused the enamel fault. Hence, a study was begun to determine the correlation of cerebral disorders and enamel faults. If a correlation exists, the observed enamel faults in combination with suspected causal events from the medical history may allow a more accurate dating of the onset of the cerebral disorder.

The formation of enamel matrix by ameloblasts proceeds in a regular fashion, beginning on the primary central incisors in the 4th fetal month and finishing on the permanent third molars in the 12th year. Matrix formation begins on the tips of the tooth cusps and is deposited progressively from the dentinoenamel junction outward and downward until the entire crown is covered. As enamel matrix is formed, the process of maturation begins, calcium salts being deposited within the matrix in a direction normal to the long axis of the tooth. Enamel differs from most other tissues in that, once formed, it cannot be remolded or reorganized but remains unchanged. Enamel, of course, may be damaged by abrasion or caries. Ameloblasts while actively forming enamel matrix may be sensitive to deleterious changes in body metabolism. It is suspected that when impoverished of oxygen or other materials, or when intoxicated, these cells fail to form enamel matrix properly, leaving a defect, a record, inscribed in the tooth enamel. The position of the defect on the teeth provides an indication of the time and the duration that ameloblastic activity was suppressed.

Enamel defects were observed at least as early as 1881, when Magitat [2] described honeycombed teeth. He thought that the defects he observed in children were caused by infantile (eclamptic) convulsions. Kronfeld and Schour,[3] in 1947, defined enamel hypoplasia as a deficient or arrested state of enamel formation, the results of interference with the metabolism of ameloblasts, manifested by irregularities and indentations on the enamel surface. The causes of enamel hypoplasia have been studied by several investigators.[4,5] Sarnat and Schour found no enamel hypoplasia in a group of 60 patients, whose medical histories were known in detail, who had had childhood diseases, including diarrhea, vomiting, diphtheria, or pneumonia. These observers did see a possible correlation between enamel defects and rickets. Twelve of their patients who had enamel defects also had convulsions. Kronfeld and Schour [3] noted pronounced neonatal enamel hypoplasia in one

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Fig. 1.—Prenatal enamel hypoplasia in child with spastic diplegia. Hypoplasia occurred in the seventh month of gestation.

child who had spastic diplegia and in another who was hemiplegic.

Kreshover et al.[7-11] produced prenatal enamel hypoplasia repeatedly in rodents given artificially induced fever, alloxan diabetes, injections of tubercle bacilli and the viruses of vaccinia, and lymphocytic choriomeningitis. The enamel hypoplasia produced was visibly and microscopically similar to that seen in humans. Thus, Kreshover demonstrated that numerous factors may cause enamel hypoplasia. Marshall-Day [12] found no evidence of prenatal hypoplasia in seven children whose mothers suffered severely from rickets during pregnancy. The inference drawn from these observations was that the fetus extracts materials sufficient for its development, even though the mother suffers from severe dietary deficiency. Forrester and Miller [13,14] found enamel hypoplasia in 13 cases of kernicterus. They also noted that the sites of hypoplasia on the teeth were related to the age at which metabolism was disturbed. The age of the person when hypoplasia occurred was estimated by Sarnat and Schour [6] and by Kronfeld and Schour.[3] These authors reported that prenatal enamel hypoplasia was extremely rare, hypoplasia in their cases occurring from the neonatal period to the third year of life.

Method

Detailed information concerning heredity, gestation, birth, and subsequent development was obtained by one investigator from the parents or medical records of 100 children who had definite indications of cerebral dysfunction. The children were examined by clinical and laboratory means. The teeth of these children were then examined by the other investigator, and data concerning the location and type of enamel faults were tabulated. In addition, the teeth of 100 apparently normal children were examined. Those who had enamel faults were examined to determine whether they had neurological disorders. The birth histories of 40 of the normal children were obtained from medical records made at the time of birth

Fig. 2.—Side view of same case shown in Figure 1.

Fig. 3.—Neonatal enamel hypoplasia. Hypoplasia occurred at the end of the ninth month of gestation, at birth.

so that a comparison of possible etiological factors could be made.

A child was considered to have hypoplasia if a defect in the enamel was observed which was characterized by a grooved ring of visible and palpable depth about the crown of the tooth. The defect could be either smooth or pitted, discolored or not discolored. Hypoplasia was considered to be distinct from hypomaturation. With the help of the developmental dentition chart formulated by Logan and Kronfeld,[16] the approximate age of a child when the fault took place was determined. Hypoplasia was considered to have occurred in prenatal time when the defects observed were on the incisal four-fifths of the primary central and lateral incisors (Figs. 1 and 2). Defects were considered to have occurred in the neonatal period when they were observed one-third of the way from the cusp tips to the cervical line of the crowns of the upper and lower first primary molars (Fig. 3). Defects occurring in postnatal time were not included, since this study was designed to evaluate earlier disorders (Fig. 4).

Results

The incidence of enamel hypoplasia in the group of 100 normal children was 10% (Table 1). The incidence of enamel hypoplasia in the group of 100 children with cerebral disorders was 68%. Comparison of the two groups revealed a χ^2 value of 58.84, indicating a P value considerably less than 0.001. In no instance was prenatal enamel hypoplasia observed in the group of normal children, but 19% of the group with cerebral disorders had enamel hypoplasia in a position on the teeth indicating its appearance in prenatal life. If children whose prenatal enamel had been lost were deducted, the proportion of patients with prenatal enamel hypoplasia in the abnormal group was 22%. Statistical analysis of the distribution of prenatal enamel faults among the normal and abnormal children revealed a χ^2 value of 24.9, which gives a P value of far less than 0.001.

All of the children who had spastic diplegia or bilateral athetotic movements (12 and 5 cases, respectively) had enamel hypoplasia. The lowest incidence of enamel

Fig. 4.—Postnatal enamel hypoplasia. Hypoplasia occurred at the end of the first year of life, following meningitis.

TABLE 1.—*Distribution of Enamel Hypoplasia Among Normal and Abnormal Children*

Manifestations of Cerebral Disorder	Neonatal			Prenatal			Neonatal and/or Prenatal	Total Cases
	Hypoplasia	No Hypoplasia	No Data	Hypoplasia	No Hypoplasia	No. Data	Hypoplasia	
Athetotic	5	0	0	0	5	0	5	5
Spastic diplegia	10	2	0	3	8	1	12	12
Hemiparesis	6	8	0	1	9	4	6	14
Epilepsies	12	10	0	2	16	4	13	22
Oligophrenia	9	9	1	4	10	5	10	19
Combined disorders	16	10	2	9	18	1	22	28
Total abnormal	58	39	3	19	66	15	68	100
Normal children	10	90	0	0	100	0	10	100

hypoplasia was seen in those cases with evidence of localized cerebral lesions manifested by hemiparesis (43% of 14 cases). Chi-square analysis of the incidence of hypoplasia in the spastic diplegia and hemiplegia groups showed a P value less than 0.001; $\chi^2 = 13.79$.

The data were analyzed to see if prenatal and paranatal events were related to the occurrence of enamel hypoplasia (Table 2). The potentially brain-damaging events considered were erythroblastosis, prematurity, bleeding during pregnancy, toxemia, and abnormal mechanisms of delivery, which included breech presentation, multiple birth, prolonged labor, the use of midforceps, and cesarean section. Also considered was a poor respiratory response of the newborn infant. A total of 67 out of 92 of the abnormal children had a history of potentially brain-damaging events; 44 of these had enamel hypoplasia. There were 7 out of 40 of the normal children who had experienced one of the events; 2 of these had enamel hypoplasia. When comparing the incidence of enamel hypoplasia between the group of abnormal children in which one or more of the events had occurred and the group of abnormal children in which none of the events had occurred, a χ^2 value of 6.81 was found, suggesting the difference could be due to chance operating alone less than 1 time in 100 and that a correlation may exist between enamel hypoplasia and the occurrence of the considered causal events.

Comment

A definite relationship between congenital cerebral disorders and enamel hypoplasia was found. Both brain and enamel might have been damaged by the same injurious process, or the enamel might have been made defective by metabolic disturbances caused by the injured brain, the brain injury having been produced by agencies which did not affect the ameloblasts directly. Perhaps the relationship of hypoplasia to cerebral disorder is direct in one case and indirect in another. Evidence was found indicating that the cerebral disorders and enamel defects were established simultaneously; for

TABLE 2.—*Relationship of Enamel Hypoplasia According to Some Possible Causal Events*

Causal Event	Neonatal			Prenatal			Neonatal and/or Prenatal	Total Cases
	Hypoplasia	No Hypoplasia	No Data	Hypoplasia	No Hypoplasia	No Data	Hypoplasia	
Erythroblastosis	4	0	0	0	4	0	4	4
Prematurity	10	9	1	3	15	2	12	20
Bleeding	10	8	0	7	9	2	12	18
Toxemia	5	3	1	2	6	1	6	9
Abnormal delivery	12	12	0	2	18	4	13	24
Poor response at birth	28	11	0	5	28	6	29	39
Abnormals with causal events	39	27	1	11	45	11	44	67
Abnormals with no causal events	19	12	2	8	21	4	9	25
Normal children with causal events	2	5	0	0	7	0	2	7
Normal children with no causal events	2	31	0	0	33	0	2	33

many persons having both conditions had a history of a definite disturbance during gestation or at birth coinciding with the time when the enamel fault was formed. Histories failed to disclose any indication of trouble during gestation or parturition in 24 cases, although definite enamel hypoplasia and obvious cerebral abnormalities were present. Either the histories in these cases were inaccurate or subtle causes were overlooked. The possibility that there exist undiscovered mechanisms causing brain damage and enamel hypoplasia should be kept in mind.

The very high incidence of enamel hypoplasia in patients who had spastic diplegia suggests that this is associated with metabolic disturbances, perhaps hypoxia, which in most instances may also contribute to the production of enamel hypoplasia. In contrast, the relatively low incidence of enamel hypoplasia in patients who had hemiparesis suggests that the brain-damaging factor is not of the proper character or magnitude to cause abnormal amelogenesis. The enamel defects in some of these cases possibly were produced as a result of the cerebral disorder. No definite relationships have been worked out as yet between enamel hypoplasia and particular potential brain-damaging factors. Another interesting point, deserving further study, concerns the high incidence, 19%, of prenatal enamel hypoplasia in the abnormal children studied. Perhaps ameloblasts are not as resistant to damage in utero as has heretofore been suspected.

Summary

The incidence of enamel hypoplasia was found to be 68% in children who have congenital cerebral disorders of all types, as compared with 10% observed in normal children. The χ^2 estimation of statistical significance suggests this difference could be due to chance operating alone less than 1 time in 100,000.

The rate of enamel hypoplasia—neonatal, prenatal, or both—observed for each manifestation of cerebral disorder was found to be as follows: athetosis, 100% of 5 cases; spastic diplegia, 100% of 12 cases; hemiplegia, 43% of 14 cases; the epilepsies, 54% of 22 cases; oligophrenia, 52% of 19 cases; combined disorders, 79% of 28 cases.

The time when enamel defects occurred was determined.

There was a correspondence between the time of occurrence of enamel defects and of potentially brain-damaging events in 44 of 67 abnormal children.

Prenatal enamel hypoplasia was observed on the primary incisors of 19% of the abnormal children.

Enamel hypoplasia may serve as an indicator, in children who have congenital brain disorders, of the time that the cerebral disorder was established.

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The Value of a Psychiatric Consultant in Training Pediatric Residents

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Introduction

A pediatrician's training should prepare him to deal with the emotional disorders of children which will form a significant part of his practice. His training should prepare the pediatrician to decide which of these disorders are best handled by him and should provide him with experience in managing patients with such emotional disorders. Through his training he should become familiar with those problems which require specialized treatment and with the type of specialized treatment most suitable for a particular case. We shall briefly review the approaches others have taken toward providing this type of training at the pediatric resident level. Then we shall describe our own approach, which consists of seeing children and parents in psychiatric consultation with residents in a pediatric outpatient department. Our case material consists of children who are currently patients of the pediatric residents referring them for consultation. In our roles of psychiatric consultants we attempt, by demonstrations of play sessions with children and interviews with parents, to teach the pediatric residents simple diagnostic techniques of value in determining the types and severity of the emotional disorders presented by many of their patients. Once the diagnosis has been established, we work with the pediatric resident in deciding which children he should continue to treat himself, which should be referred to the child psychatric clinic of our hospital, and which should be referred to other clinics or agencies. The pediatric resident learns the criteria on which such a decision is based, since he participates actively with the psychiatric consultant in the play session with the child and interview of the parents. In the case of a child whose emotional difficulties are to be managed by the pediatric resident, the psychiatric consultant helps the resident learn ways of handling such problems. We encourage the pediatric resident to see such a parent-child unit regularly and to use the psychiatric consultant in a teaching and supervisory capacity.

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Historical Review

In reviewing the course of the development of child-guidance clinics in America, Gardner [1] points out that the establishment of the hospital-affiliated child-psychiatry clinic came about both through the emphasis on the importance of psychiatry in adult medicine and the expressed needs of the pediatricians who had been dealing with children for many years. Coincident with this, the need for adequate and meaningful experience in the handling of emotional problems of childhood at the resident level has come to have a prominent place in the pediatric training regimen. Although the first child-guidance clinic in this country was established by Dr. William Healy, in 1909, it was not until 1921 that the first child-guidance service associated with a pediatric teaching center was established, at the University of California. Langford and Wickman [2] traced the development of the psychiatric service in pediatric teaching centers and pointed out that this develop-

ment has come about in two different ways: first, through the establishment of a child-psychiatry clinic within a pediatric service and, second, as a further development and extension of an already developed clinical service at the institution. As an example of the second method of development, the Child Psychiatry Clinic at the Children's Medical Center, in Boston first developed in the early 1930's as an outgrowth of the interest in neurological problems of childhood, which gradually spread to include the psychological factors. As Langford and Wickman [2] point out, the goal is "to orient the pediatrician-in-training, the medical student, and the staff member so that he will be better prepared to recognize the importance of this aspect of the child's growing up process, and to give him some of the tools with which to handle problems more adequately and to prevent, if possible, the development of future problems in his child patients." The methods and areas in which this training can take place are manifold and include inpatient and outpatient work at both a medical student and a graduate level. The methods used in the various teaching centers throughout the country, as described by Langford and Wickman,[2] Tisza and Richardson,[3] and Senn,[4,5] generally include an over-all program, with the main emphasis on informal discussions of general topics, brief psychiatric consultations, formal conferences and seminars, rotation of the pediatric resident through the child psychiatry service, participation in ward rounds, and inclusion of the child psychiatrist as a member of the team with responsibility for the care of the inpatient child. Other authors who have dealt with the problem of integrating psychiatric knowledge with pediatric training are Pearson,[6] Kanner,[7] Huschka,[8] Bibring,[9] and Weisner.[10]

It is our purpose in the present communication to describe and discuss one of these methods, namely, the use of the consultation as a teaching device. Similar programs have been described by Senn [5] at the Child Study Center of Yale University, and by Langford and Wickman [2] at Babies' Hospital, in New York. As a result of this experience Senn [5] believes that didactic learning of content alone cannot be fostered unless the pediatrician has the opportunity for experiencing a relationship with the consultant and that acquiring insight into psychiatric problems comes best with the establishment of a satisfactory interpersonal relationship between consultant and pediatrician. We are in full agreement with this and believe that the use of the consultation interview, both as an opportunity for supervised observation of the complex interplay of emotional factors and as a means to foster the development of a satisfactory relationship between consultant and pediatrician, can make this a meaningful learning experience for the pediatrician in training.

Description of Teaching Method

We are both child psychiatrists. Each of us spends every weekday morning seeing parents and children in consultation together with the pediatric residents who staff a pediatric outpatient department. In addition to the pediatric fellows and residents, several clinical psychologists and a medical social worker are available each morning for psychological testing and medical case work, respectively. The psychologist or medical social worker may be requested to see a given child or parent either by the pediatrician or by the psychiatric consultant.

Our chief function is to teach the pediatric house officers and fellows to deal competently with the emotional problems of children which they see so frequently during their pediatric training and which will constitute a significant part of their pediatric practice in future years. Our method is to see parents and children in consultation with any pediatric resident from the hospital. In all cases the resident has taken a history and formed an initial impression of the child and parent.

Each consultation consumes about 45 minutes. The first step in the consultation procedure is the discussion of the case by

the pediatrician and the psychiatric consultant. The pertinent problems are outlined, and the areas to be investigated during the consultation procedure are defined. Next, the resident introduces the psychiatrist to the child and parent. Usually the child remains in the waiting room while the parent is interviewed by the consultant and resident.

Parenthetically, we have been both surprised and pleased by the readiness with which almost all parents and children have accepted being interviewed by a child psychiatrist. We assume that this accepting attitude results both from the ever-increasing enlightenment in the community concerning child psychiatry and from the skill and tact with which the resident presents to the child and his parent the idea of consultation with the child psychiatrist.

After interviewing the parent, the resident and the psychiatrist observe, play with, and talk to the child. We have available a variety of play materials appropriate for boys and girls ranging in age from infancy to early adolescence. The type of play material chosen and the use made of such material by the child has been of help in determining the type and severity of the child's emotional disturbance. In addition, we have attempted to teach the pediatrician how, by observing a child's play, he can form at least a rough idea concerning that child's emotional and intellectual status.

The teaching value of such techniques is best illustrated by the specific clinical material in the next section of this paper.

Following the initial discussion by the pediatrician and the psychiatric consultant, the interview with the parent, and the interview with the child, the pediatrician and consultant together decide how further to treat the patient. We believe that the well-trained pediatrician is competent to handle most of the emotional problems which arise in his patients. In our work we attempt to show the pediatric resident how, by the use of sympathetic listening, intelligent explanation, constructive reassurance, and advice concerning environmental manipulations, he can successfully manage most of the emotional problems which occur in his patients. We participated in more than 500 consultations in the first year of our work. Of these, about 80% of the cases have continued to be followed by the resident and have not been referred either to a psychiatric clinic or to another agency. When a child whom the resident and psychiatrist saw together in consultation continues to be followed by the pediatrician, the psychiatrist encourages further discussion with the resident from time to time about the case. Occasionally the psychiatrist will, after the child has been followed for a time by the pediatrician, again see the parent and child in follow-up consultation with the pediatrician.

The consultants have referred about 10% of the children whom they have seen to the psychiatric clinic of the Children's Medical Center. These children are then studied by the type of diagnostic procedure employed by most psychiatric clinics for children. The child is interviewed by a psychiatrist and tested by a clinical psychologist. A psychiatric social worker talks with at least one of the parents. Then a diagnostic conference is held at which the psychiatrist, psychologist, and social worker present their findings. At the diagnostic conference a decision is made regarding psychiatric treatment or other disposition of the case. We have encouraged the referring resident to participate in the diagnostic conference. Such participation often furnishes the psychiatric clinic with valuable information about the family being studied. In addition, this provides an opportunity for the pediatric resident to learn about the structure and function of a psychiatric clinic for children. By participating in the diagnostic conference, the resident can learn more than was possible in the psychiatric consultation about the psychodynamics of his patient.

The third group, comprising about 10% of the consultations we have done, is made up of those cases we have referred to other agencies. Some of these we have referred to

family-case-work agencies for such services as family counselling for the parents, play and activity groups for the children, placement in summer camps, and so forth. A few children from extremely disturbed home situations we have referred directly to child-placement agencies. Occasionally we have sent a psychotic child to a hospital for in-patient psychiatric treatment. Certain children we have referred to psychiatric clinics with specialized facilities for treating pre-school children, children with learning problems, adolescents, delinquents, and so forth.

We have consulted with schools about special class programs and manipulation of the school environment. A medical social worker is available for discussing these referrals with parents and for contacting the agencies involved. Dealing with this third group of children has helped to acquaint the residents with the various community child-care facilities located apart from pediatric hospitals. In addition, the residents have learned how to utilize these facilities effectively.

Several clinical psychologists participate in the "consultation-teaching" program. Through discussions with the psychiatric consultants, the residents have learned to utilize psychological testing in an effective manner. Now, instead of merely requesting psychological testing of a child, many of the pediatric residents will specify the nature of the particular problem in which they are interested. They will ask for tests to determine the type of emotional problem in their patient, or to determine his intelligence, or to explore the possibility of brain damage.

Case Illustrations

The following cases, selected from the children seen in consultation, serve to illustrate the use made of the consultation service, its value in acquainting the resident with the criteria for psychotherapy, and the various resources for disposition following consultation. The cases are divided into three groups as follows.

Group 1.—This group includes cases which were followed in the outpatient department by the resident, in which it was felt that the symptom did not represent a basic neurotic disturbance nor was the symptom interfering with the child's general favorable adjustment to his family and environment. These cases were handled by the resident using the techniques described above.

The educational value of the "consultation teaching" in this group of cases is twofold. First, these cases illustrate criteria which the pediatric resident learns to employ in deciding which emotional disorders in his patient he should manage himself and which should be referred to a psychiatrist. Second, as he follows such cases the resident learns from the psychiatric consultant various techniques which will be useful to him in his own pediatric practice. The educational value of this group of cases is particularly great, since in his practice the pediatric resident will manage most of his patients with emotional problems rather than referring them for specialized treatment.

CASE 1A.—A 10-year-old boy was brought to the outpatient department because of severe headaches and an accompanying feeling of stiffness of the neck. The headaches had their onset about two or three months prior to the hospital visit, at a time when the patient's mother had been very tense and anxious about a move the family was to make. A medical work-up was negative. The mother was exceptionally anxious, believing that her child had a brain tumor despite the fact that she had been reassured by one other physician that this was not the case. In other areas, as revealed in the consultation interview, the patient seemed to be successful and well-adjusted. When entering the interview with the psychiatric consultant and the pediatric resident, he seemed to show an appropriate amount of anxiety over this new situation, but he was able to respond warmly once the purpose and nature of the interview were explained to him. He neither denied nor overemphasized his symptoms and was able to describe them clearly and coherently, at the same time welcoming the opportunity to talk to adults with an objective viewpoint. He did not choose to play with toys or to avoid direct questions about such things as his relationships to his peers, his school achievement, or difficulties at home with his parents, particularly his mother. His answers revealed that he socialized well, that he had many friends that he was able to identify with in a

masculine way, and that his school achievement and ability to concentrate had not been interfered with by anxiety or exaggerated fantasy life. His ability to meet and to cope with the new and stressful situation of the consultation interview in a way adequate for his age, while giving relevant information concerning the production of his symptoms, indicated a basically sound personality structure and good reality testing with sound ego mechanisms. He volunteered the information, when asked what he could tell us concerning why he thought he got the headaches, that he was sure it was when he was at home and mother would begin "to worry about me or yell about the house." He further said that he never got the headaches when away from home. He told the interviewers with great enthusiasm and pride of his athletic achievements and of his especial liking for baseball, in which he was an outstanding member of his Little League team. It seemed clear that this was not a crippling symptom nor one that was interfering with his general development in other areas. It was decided to follow the mother and child in the outpatient department, to have them see the pediatric resident at intervals, and to use the techniques of constructive environmental manipulation and of reassurance for the mother, helping her to see how her anxiety seemed to reflect onto the child. At the same time, the patient was reassured concerning his symptom and was given the opportunity to talk with the pediatrician at each visit. With the institution of this type of management the headaches abated considerably and finally disappeared. No new symptom appeared, and his adjustment continued to be satisfactory.

CASE 1B.—A mother brought her son to the hospital specifically requesting to have him seen by a psychiatrist. The patient, 8 years old, had recently developed compulsions to tap certain objects and to have his curtains, bedspread, and shoes arranged in certain ways in his room. In general, he seemed a healthy boy. None of his compulsions had affected his adjustment with his family, with his friends, or at school. We explained to the mother that her son's behavior was well within normal limits, that a few transitory compulsive symptoms were usual at his age, and that psychiatric treatment for her son was not indicated. At this point, the mother expressed tremendous relief and told us that she had feared her child was "going crazy." Further discussion revealed that the patient's uncle had recently been hospitalized for a psychosis, the precursors of which had been severe compulsions. This had precipitated the mother's fear of psychosis in her child. This case was of teaching value in that it led to a discussion between the pediatrician and consultant about the criteria for recommending that a child receive psychiatric treatment.

Group 2.—This group includes children in whom clear-cut indications for psychotherapy were seen as a result of the consultation. These were cases in which the symptom was obviously interfering with the developmental progress and adjustment of the child and where unconscious alterations had taken place, thus removing the symptom from the availability of direct approach. These children were referred to the child psychiatry clinic.

This group is of educational value because the cases illustrate for the pediatric resident the criteria he can use in deciding which of his patients with emotional disorders require psychiatric treatment. Because there is a shortage of facilities for psychiatric treatment of children in most communities, an educational program which teaches pediatric residents to select children who can benefit most from psychiatric treatment is especially important at this time. These cases are also of educational value, because they provide the psychiatric consultant with opportunities for demonstrating techniques of presenting to parents the advisability of psychiatric treatment for their child. The parents' attitude toward such treatment is one of the factors which determines the success or failure of the treatment,[11] and one of the functions of the psychiatric consultant is to help the pediatric resident learn ways of instilling positive motivation for treatment in parents and thus also in their children.

CASE 2A.—An 8-year-old girl was referred because of fear of going to school, accompanied by nausea and vomiting in the mornings. The history, taken by the pediatric resident, revealed a sudden onset at the beginning of the school term, about two months prior to the medical outpatient department visit. At this time she complained of "sickness" in the morning and would scream and cling to her mother when asked to go into the school room. The symptoms had progressed to the point where, at the time of consultation, the patient was totally unable to go to school and was staying home all day. Her behavior while at home was normal and presented no problems. The medical findings were entirely negative; therefore, consultation with the child psychiatrist was requested by the pediatric resident. By talking with the child and her mother, it was possible to ascertain

the close connection between the morbid fear of school and reality factors such as a recent severe illness in the patient's grandmother, which seemed to be a precipitating element. The mother also felt this child had been, since she was the youngest sibling, "closer to me" than any of her other children. Since the appearance of the symptom indicated an unconscious displacement of anxiety from intrapsychic conflicts onto the school situation, she was referred to the psychiatry clinic, where a diagnosis of acute school phobia was made and psychotherapy was instituted. The history as obtained in this case represents a fairly classical example of a school phobia in a child, a condition that has been recognized and described with increasing frequency by many child psychiatrists in the past 10 years. Generally speaking, the dynamics of this reaction follow the pattern seen in any phobia or morbid fear of a situation or object without adequate reality reason. In such a situation, the child has an unconscious dread or fear of often a totally unrelated object or situation, accompanied perhaps by intolerable aggressive or hostile wishes on the part of the child toward that object or situation. Consciously, the child handles this by externalizing and displacing the fear onto another situation, which may perhaps have some associative connections with the original feared situation. Thus, the real fear is not recognized by the child, but another situation is treated as if it were the dangerous one. In this case, as a result of psychotherapy, it became apparent that the real fear of the child was that fantasy of the possible death of her mother, stemming from talk of death and mother's obvious worry when the grandmother became ill. This was seen by the child as in part occurring as punishment to herself for various situations in which she had been angry with her mother and jealous of her older sisters. As a result the whole conflict had been repressed, and the fear had been displaced onto the school, where the teacher represented a mother-figure. This reconstruction obviously was not possible at the time of the consultation interview; what was apparent at that time was that the dread of going to school was not commensurate with the reality situation and that the child was not conscious of the connecting links between her repressed fears and the school situation. Therapy was carried out in the child-psychiatry clinic with both child and mother being seen, the child by a psychiatrist and the mother by a psychiatric social worker. At the end of four months' treatment, during which time the child and the mother had come to see the original feared situation and the mother had been able to reassure the child, the phobic reaction had disappeared and the child was able spontaneously to attend school again.

Case 2B.—An 8-year-old girl, was brought to the hospital with a chief complaint of nausea, fear of vomiting, and the gradually increasing inability to eat. At the time of the visit the patient was eating literally nothing and had lost 10 lb. within the previous month; she complained of constant nausea and was always aware of being afraid she would vomit. Associated with this fear were many other fears, necessitating a general inhibition of her activity. For instance, she had to call her mother from school several times a day, especially about noontime, when she would be faced with the problem of having to eat in the school lunchroom. She would call her mother to be reassured that it was all right to go ahead and try to eat. Other phobic prohibitions had developed—she wore the same dress constantly for fear she would be sick if she changed and wore another; she would insist on wearing the same pair of pajamas at night, for the same reason. The history revealed that the patient had always had problems associated with the gastrointestinal tract. She had had a feeding problem in infancy, causing a great deal of anxiety in the mother when she would refuse her formula or spit up. She had screeched with pain during her bowel movements even though, according to the mother, her stools were regular and not hard in consistency. The other members of the family, especially the mother, exhibited phobic concerns about food and eating. The mother had frequently gone on rather bizarre restricted diets in order to relieve phobic fears of cancer, etc. A complete physical work-up, including barium studies, was entirely negative, and psychiatric consultation was requested by the pediatric resident. During the consultation interview the patient proved to be a very alert, intelligent, and verbal child. Even before she entered the playroom she began to talk in a rapid, tense voice, saying that she was afraid to eat and that if she ate she would vomit. In response to a question as to what she thought was wrong with her, she made rapid and confused statements to the effect that she knew there was nothing wrong inside her, but this did not keep her from being afraid as if something awful would happen. Immediately following this, she said that her father had something wrong with his nose and the doctors had to operate on it. She went on to say that she wanted very much "to be not afraid" and to find out what was wrong that made her so afraid. She used the dolls and doll house to illustrate a situation in which a little girl was alternately punished and chased out of the house because she was so bad. All of this activity was quite spontaneous, and the child appeared to be under great pressure to find a means of expression of her difficulties. Usually in a child of this age such obvious fears and associations would not be talked about or played out, especially in the first play interview. This child freely verbalized her need to have an ally in the

therapist against her fears and also indicated quite directly that her fear was alien to her and she would like to be rid of it, while recognizing that the fear was due to "feelings" and did not have a reality basis. This wish to get well and insight into the nature of her illness, as well as her ability to relate in a trustful way to the interviewers, indicated that she could benefit greatly from psychotherapy. As a further and perhaps more primary indication, the symptom itself is to be considered. Since the nature and severity of the anorexia posed a definite physical threat to life and were of an emotional etiology not modifiable by superficial means, psychotherapy became not only the treatment of choice but also the only means by which the symptom could be modified.

Group 3.—Included in this group are cases referred to agencies or clinics other than the psychiatric clinic of the Children's Medical Center. Such referrals were made for a variety of reasons, including basic disturbance in family relationships to which the child is reacting, the necessity for specialized clinic setting depending on the age of the child or the specificity of the symptom, or the need for a more controlled environmental setting.

The educational value of this group of cases, like that of Group 1 and Group 2, is twofold. These cases provide the pediatric resident and the consultant with examples of children who can best be helped by facilities other than those available in a children's hospital. Probably more important are the opportunities which this group gives the psychiatric consultant to acquaint the resident with the multitude of clinics and agencies available in many communities to help children and parents with emotional problems. Through our teaching we have helped the pediatric residents to make full use, in appropriate cases, of these community resources.

Case 3A.—A 4-year-old girl was brought to the hospital with the chief complaint of acute loss of speech, soiling, wetting, and panic on separation from her mother. The mother stated that all these symptoms appeared suddenly after a move the family made about two weeks prior to the hospital visit. Other symptoms included phobic-like reactions to any new situation and a sudden abandoning of play with toys which she had previously enjoyed. When all organic determinants had been ruled out by physical and neurological examinations, the parent and child were seen in consultation with the pediatric resident. The history taken by the resident had revealed a normal developmental pattern for this little girl up to the time of the move, which was obviously traumatic for the child. As a result of the observations and discussions between the pediatrician and psychiatrist, it was felt that this represented an acute regression in response to a traumatic experience and that intensive psychiatric treatment was indicated. The exaggerated response to the move seemed to be due to a combination of factors having to do with both the child's previous adjustment and the reactions of the mother concerning the change of houses. Usually, a child of this age will exhibit some transient anxieties or regressions when a move takes place but quickly establishes a satisfactory adjustment to the changes that have been made. This little girl obviously showed disturbance in all areas of behavior, which showed no signs of abating. With this in mind, a second and more careful history was taken, which revealed that the child had shown indications of a disturbed relationship to her mother and a sort of "turning to objects" even prior to the move. It looked as though the actual house in which she lived and her special room, toys, etc., had come to represent security to her, rather than the actual persons in in her family. Thus the complete change and rearrangement of these things was excessively disturbing. Another factor, which the mother herself recognized, was the overconcern of the whole family, especially the mother, about not damaging or marring the walls or furniture in the new house. There had been a good deal of talk and reminding from the mother that the child was to be very careful and not scratch or break anything when they moved, so that an atmosphere of anxiety and tension concerning the move was built up. The child was referred to a clinic specializing in the treatment of pre-school-age children. Improvement was marked as soon as treatment commenced; the patient began to talk and communicate, slowly at first and then more rapidly; the other manifestations of regressive behavior were given up within a relatively short time as she continued in treatment.

Case 2B.—The patient's parents brought him to the hospital because they wanted help in dealing with his stubborn and defiant behavior. This boy, 7 years old, got along well in all situations except when he was with his parents. Then he behaved like a "spoiled brat." When seen with his parents the patient lived up to their description of his behavior at home. However, when just the child, the pediatrician, and the consultant were together, the patient's behavior was entirely within normal limits. Even as they described their son his parents began to argue. It was evident that they disagreed

about most phases of his upbringing and had made no effort to conceal these disagreements when they dealt with their child. The primary problem seemed to be conflict between the parents. The patient himself, except for the expected reaction to this conflict, appeared to be a relatively normal 7-year-old child. Therefore, the parents were referred to a family service agency for help with their own problems.

Comment

The steadily increasing demand for psychiatric consultations and the fact that we performed about 500 such consultations during the first year of our work indicate that our method is a useful one. The effectiveness of our teaching method is due to the opportunity it provides for pediatricians to interview, observe, and discuss their patients with the psychiatric consultants.

In order to maintain the effectiveness of such a teaching method it is most desirable that the consultants see the patients at the time they are referred and that the residents have adequate time to participate in the "consultation teaching." A psychiatric clinic associated with such a teaching program is necessary to provide psychotherapy for those cases where this is indicated.

Summary

We stress the importance of teaching pediatric residents to recognize and manage emotional problems in their patients. After reviewing others' methods of providing such training, we describe a method which we employ. This consists of using psychiatric "consultation teaching" in a pediatric outpatient department. By the use of case material we illustrate the three categories in which, from the point of view of management, children with emotional disorders can be classified. These are as follows: Group 1—cases which should be followed by the pediatrician; Group 2—cases where clear-cut indications for psychotherapy for the child are present; Group 3—cases which should be referred, because of specialized problems, to clinics or agencies other than general child psychiatry clinics. The use of such a scheme of classification has enhanced the educational value of our teaching method. This scheme provides a tool which the resident learns to use, with the help of the psychiatric consultant, in managing children with emotional disorders and one which the resident can use later in his own pediatric practice. We believe that this method of teaching the handling of emotional problems in children is effective because of the opportunity it affords for close collaboration between the pediatric resident and child psychiatrist.

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The Incidence of Infantile Pyloric Stenosis

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We were able to find in the literature only five surveys which report the incidence of congenital hypertrophic pyloric stenosis per number of live births for a given area. Wallgren [1] found an incidence of 0.4% in Sweden. Two separate studies registered a frequency of 0.3% in England.[2,3] In Scotland the incidence was found to be 0.15%.[4] A fifth survey, coming from Israel,[5] reports an incidence of 0.05%.

Most pediatric textbooks mention the rarity of congenital hypertrophic pyloric stenosis among Negroes,[6,7] although they do not provide actual figures. Wallgren [1] also mentions the infrequency of this disease entity in Latin countries and in Turkey. Field [8] made the same observation for Malaya. Hypertrophic pyloric stenosis has never been reported in an Australian aborigine.[9] In the Siriraj Hospital in Bangkok, Thailand, only one case was registered among 9676 pediatric admissions during the period 1953-1955.[10] The low incidence in Israel seems to confirm the above-cited impressions that the frequency of infantile hypertrophic pyloric stenosis differs in various populations.

The present investigation was designed to study the incidence of infantile hypertrophic pyloric stenosis in a community in the United States, with special attention to the incidence in Jews and Negroes in this population group.

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Material

The records were reviewed of all but two cases* of congenital hypertrophic pyloric stenosis proven by operation or autopsy in infants whose parents were residents of Pittsburgh and some of its adjacent areas. A period of 11 years, 1945-1955 inclusive, was studied.† All the hospitals of the

*Two charts in one hospital were not made available and are therefore excluded from the study.

† In one hospital there was no index for the years 1945 through 1952. From the number of cases in the years studied in this hospital, it is likely that no more than four or five were missed. It is very questionable that any of them would have been Negro.

TABLE 1.—*Number of Live Births and Incidence of Infantile Pyloric Stenosis in the White and Negro Population of Pittsburgh*

	White Population			Negro Population		
	Live Births, No.	Cases of Infantile Pyloric Stenosis, No.	Incidence of Infantile Pyloric Stenosis Per 100 Live Births	Live Births No.	Cases of Infantile Pyloric Stenosis, No.	Incidence of Infantile Pyloric Stenosis Per 100 Live Births
1945	9,160	7	0.0765	1,390	--	
1946	12,183	19	0.156	1,611	--	
1947	13,423	22	0.164	1,874	1	0.0535
1948	11,930	21	0.175	2,013	--	
1949	11,739	9	0.0765	2,193	2	0.0912
1950	11,565	15	0.13	2,085	1	0.048
1951	11,946	20	0.167	2,252	3	0.133
1952	11,801	13	0.11	2,211	--	
1953	11,518	14	0.123	2,276	2	0.088
1954	11,239	9	0.08	2,427	1	0.041
1955	11,525	4	0.035	2,477	1	0.040
11 years	127,029	163		22,909	11	
Mean incidence ± S. D.	0.12% ± 0.046			0.046% ± 0.044		

area studied were surveyed, and cases were found in 11 of them. There is no reason to presume that any cases meeting the above-mentioned criteria of diagnosis could have escaped our attention. The number of resident live births for the white and the Negro populations has been obtained from the Pennsylvania State Department of Health, Statistical Methods Section.

Results

Table 1 presents the number of live births and the number of babies with congenital hypertrophic pyloric stenosis in the white and Negro populations of Pittsburgh for the years 1945-1955, inclusive. During this period, there were 127,029 white live births, with 153 cases of congenital pyloric stenosis among these babies. Calculating the incidence for each year separately, there is a range varying from 0.035% to 0.175%. The mean value for the 11 years is 0.12%, with a standard deviation of ±0.046. Expressed differently, this gives an over-all incidence of 1 case per 830 live-born white babies. During the same period of time, there were 22,809 Negro live births, with 11 cases of congenital pyloric stenosis among them. The mean incidence was 0.046%, or 1 case in every 2073 live Negro births. This difference in incidence between white and Negro babies is statistically significant ($P<0.01$). In the adjacent areas studied, there were 39,279 live white births during 1945-1955. The number of babies with congenital pyloric stenosis was 58, giving an incidence of 0.147%, or 1 case in 680 live-born white babies. In the same area, among the 2600 Negro births there was 1 case of congenital hypertrophic stenosis, or 0.038%. If the figures from Pittsburgh and its adjacent areas are added together, the combined incidence for white babies is 0.126%, or 1 case in 790 live births, and for the Negroes, 0.0485%, or 1 case in every 2100 live births. If the two cases not included in the study would have been white babies, the incidence of infantile pyloric stenosis found would be almost unaffected. If both would have been Negro the incidence in that population would have increased from 1 case in every 2100 live births to 1 case in every 1840; again, a change not significantly altering the incidence of infantile pyloric stenosis in Negro babies.

Since no data were available for the Jewish birth rate in Pittsburgh, we were obliged to take a ratio of the Jewish population to the total white population as an index for calculation of the incidence of congenital hypertrophic stenosis in Jews. In 1950 the white population of the City of Pittsburgh was 593,825.[26] In 1953, the Jewish community of the same city was estimated to be 47,000 persons.‡ Taking these figures as rough averages, the Jewish population of Pittsburgh represents about 7.9% of its white inhabitants. Among the 153 white patients with pyloric stenosis there were 10 Jewish babies, or 6.5% of the total number of cases in white babies. There was no difference in the sex ratio of affected babies between white and Negro. In the former, the males represented about 85% of the total number of cases, and in the latter, 82%.

‡ Reference 27, provided by Mr. Meyer Schwartz.

TABLE 2.—*The Incidence of Infantile Pyloric Stenosis*

Survey	Live Births, No.	Infantile Pyloric Stenosis				
		Cases, No.	Diagnosis Confirmed by	Incidence		Standard Error of Sample
				Per Cent of Live Births	Per No. of Live Births	
Göteborg, Sweden,[1] 1934–1940	25,642	102	X-ray	0.4	1:250	0.039
Newcastle-on-Tyne, England,[2] 1939–1942	17,457	49	Surgery	0.28	1:355	0.04
Birmingham, England,[3] 1942–1949		478	>90% surgery	0.3		
Dundee, Scotland,[4] 1940–1946	21,268	32	Surgery	0.15	1:665	0.026
Israel,[5] 1948–1953	196,587	108	Surgery	0.05	1:1820	0.03
Pittsburgh, 1945–1955						
White	166,308	211	Surgery	0.126	1:790	0.014
Negro	25,409	12	Surgery	0.048	1:2100	0.013

TABLE 3.—*Significance of Difference Between Observed Rates of Infantile Pyloric Stenosis in the Present and Other Studies*

	P
Pittsburgh-white/Pittsburgh-Negro	<0.01
Pittsburgh-white/Newcastle-on-Tyne	<0.01
Pittsburgh-white/Dundee	<0.5
Pittsburgh-white/Göteborg	<0.01
Pittsburgh-white/Israel	<0.02
Pittsburgh-Negro/Israel	<0.7
Dundee/Newcastle-on-Tyne	<0.05
Newcastle-on-Tyne/Göteborg	<0.1

Table 2 summarizes the incidence of infantile pyloric stenosis from the known surveys in the literature and the present study. Table 3 shows the statistical analysis of these data. There is a significant difference in incidence of infantile pyloric stenosis between the white population in Pittsburgh and the inhabitants of Newcastle-on-Tyne, Göteborg, and Israel. However, no difference is found between the white population of Pittsburgh and that of Dundee, and between the incidences among the Negroes and the Jews in Israel. The difference in incidence between Dundee and Newcastle-on-Tyne is significant.

Comment

The etiology of pyloric stenosis in early infancy is far from clarified.[11] Its congenital character has been challenged in recent years. Wallgren [12] showed by routine roentgen examination of 1000 newborns that those babies who later developed pyloric stenosis had a normal roentgenological pattern immediately after birth. The genetic inheritance of this disease plays certainly an important role. Its increased frequency in children whose parents were affected and the multiplicity of cases in certain families have been reported.[14-20] It has been calculated that among children of affected parents the incidence of infantile pyloric stenosis is as high as 6.9%.[21] In favor of the genetic factor would also be the finding of infantile pyloric stenosis in monozygous twins,[22,23] but, unfortunately, there are reports in which only one of monozygous twins was affected.[24,25] McKeown et al. in a series of papers [3,13] discussed the idea of prenatal or postnatal environmental influence upon the development of this condition.

The data in this study and in those reviewed are based on manifest cases of infantile pyloric stenosis who have come under medical care. Belief in the acuity of the diagnoses and completeness of the data presented is expressed by each author.

From the present survey, it is evident that infantile pyloric stenosis in the Negro population in Pittsburgh is significantly less frequent than in the white population of the same area. The incidence of infantile pyloric stenosis in the white population in Pittsburgh is less than half that in England or Sweden, about equal to that in Scotland, and more than double the incidence in Israel. It is interesting to note that the incidence among the Negro population in Pittsburgh equals that of the Jewish population in Israel. There is also little variation in frequency between Sweden, where diagnoses were established by roentgen examination, and England, where the data are based on diagnoses confirmed by surgery. The difference in incidence between England and Scotland is astonishing.

Genetic differences could certainly account for the findings mentioned above. From the data accumulated in this study, the magnitude of the role played by this or by some environmental factor could not be assessed.

Since the number of Jewish births in the area studied is not known, we cannot be sure that our comparison of incidence of infantile pyloric stenosis in Jews and the total population is accurate. With the method used, there was little variation between the two groups.

Further studies of this kind in other parts of the United States and other countries might help explain the difference in incidence of infantile pyloric stenosis in various parts of the world and in different populations. Such findings may be a necessary link in the understanding of the etiology of this disease.

Summary

The incidence of infantile hypertrophic pyloric stenosis has been studied in a community in the United States.

The results obtained show that 0.13% of live-born white babies are affected by this disease. The incidence in Negro babies is less than half of this. The figure for white babies is less than half of that for babies in England or Sweden, equal to that in Scotland, but more than twice of that for Israel.

Addendum

After this paper had been submitted, another report from northeast Scotland reached this country (McLean, M. M.: *Arch. Dis. Child.* 31:481, 1956). Surveying the area of Aberdeen over a 16-year period, the author found a mean incidence of infantile pyloric stenosis of 0.33% of all live births.

Dr. Robert Klein gave advice and encouragement. Harry W. Miller obtained the population statistics.

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Chloramphenicol-Tetracycline Treatment of Salmonellosis in Children

Strip-Gradient and Replica Strip-Gradient Techniques as Guides to Therapy

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Chloramphenicol treatment, today the therapy of choice against typhoid fever and other Salmonella infections, is often inadequate in that relapses are common,[1-3] the organisms persist in bile or stools for variable periods of time, carrier states may not be permanently eradicated, and the important complications of intestinal hemorrhage and perforation still may occur.[4] The use of an additional antibiotic against Salmonella infections, so that the dose of each drug might be decreased and the efficacy increased, therefore appeared to us to be a logical approach to more adequate treatment. The choice of such an additional drug would depend upon the sensitivity of salmonellae to combinations of the available antibiotics.

To assist in selection of such an antibiotic combination, many methods are available. One is that of clinical trial. Another is that of in vitro testing; commonly, the serial tube dilution and plating method.[5,6] This latter technique is accurate and would be helpful if it were not for the time and labor required to complete a single study.

In an attempt to provide a more practical method for in vitro estimation of bacterial sensitivity to antibiotic combinations, Streitfeld and Saslaw[7] described the strip-gradient technique for testing pairs of antibiotics in various concentration ratios. This procedure had the advantages of relative simplicity and greater speed. True evaluation of this laboratory approach, however, depends entirely upon the degree of correlation between in vitro observations and in vivo results.

The present investigation records the bacteriological and clinical findings in a series of patients suffering from salmonellosis. We found the combination of chloramphenicol and tetracycline to be uniformly additive or synergistic in vitro and almost uniformly effective therapeutically. However, because of the small number of cases and lack of adequate control data in our series, the efficacy of this combined therapy warrants further evaluation.

Method and Material

Salmonellae isolated from the blood or stool of 29 successive patients suffering from salmonellosis, including 5 cases of typhoid fever, at the Jackson Memorial Hospital, Miami, Fla., were studied. Cultures were provided by Dr. Alexander Kimler, bacteriologist. In addition, a culture was obtained from the pulmonary lesion of one of a colony of experimental rats ill with pulmonary and systemic salmonellosis at another hospital in this area. Through Dr. Albert Hardy, Director, Bureau of Laboratories, Florida State Board of Health, Jacksonville, 15 additional stock cultures of various groups and types of salmonellae were furnished for this study.

Each culture was checked for sensitivity to various antibiotics by a standard antibiotic disc method,[8,9] with use of blood agar base medium (Difco) and antibiotic discs (Difco). Mueller Hinton agar medium (Difco) was used for assay

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From the Department of Medical Research, National Children's Cardiac Hospital, the School of Medicine and the Department of Microbiology, University of Miami.

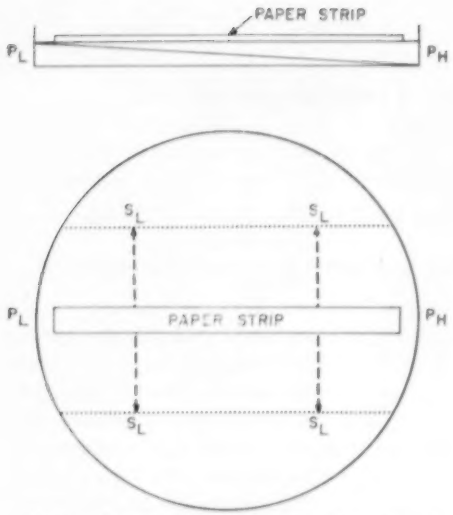


Fig. 1.—Diagrams of strip-gradient plate. PH, maximum (set) concentration of (primary) antibiotic in plate; PL, minimum concentration of (primary) antibiotic in plate; paper strip contains maximum (set) concentration of secondary antibiotic; SL, minimum concentration of (secondary) antibiotic diffused from strip.

of bacterial sensitivity to sulfadiazine. Those single drugs which were most effective in inhibiting bacterial growth around the discs were used for study in combinations with one another. Combinations of antibiotics were assayed by the strip-gradient technique.[7] This method utilized the Szybalski antibiotic gradient plate,[10] combined with an antibiotic-impregnated filter-paper strip. Antibiotics* were prepared as previously described.[7] Plates were prepared by the following technique (Fig. 1): Fifteen milliliters of blood agar base (Difco) was poured so as to cover the entire surface of a tilted Petri dish, and the agar was allowed to harden. The dish then was placed on a horizontal surface and a second layer of blood agar base (15 ml.), containing one of the antibiotics (primary) in predetermined concentration, was poured over the entire surface of the first layer of hardened agar. The new surface was permitted to harden. Since the antibiotic in the gradient plate diffused vertically so that the drug was diluted in proportion to the thickness ratio of the agar layers, a uniform antibiotic concentration slope was established. This gradient plate now contained one antibiotic varying in concentration from a high value (the predetermined concentration), where the antibiotic layer was thickest, to a very low concentration, where this layer of agar was thinnest. A loopful of an 18- to 24-hour broth culture of the organism to be tested was swabbed lightly over the surface of the entire plate. A strip of sterile Whatman filter paper No. 42, 8.8×0.8 cm., was saturated in an aqueous solution of the second antibiotic (secondary), of predetermined concentration. This strip was placed centrally on the surface of the gradient plate, so that it crossed from the low to the high primary antibiotic concentration zone. The secondary antibiotic diffused laterally from the paper strip and set up a steep concentration gradient throughout the area adjacent to the strip (Fig. 1). By this strip-gradient technique, the organism was exposed to all combination ratios resulting within the limits of the concentrations of both antibiotics selected for the test.

After 18 to 24 hours of incubation plates were read as previously described[7] and interpreted as indicated in Figure 2. This plate technique permitted the determination of the growth-inhibitory effects of pairs of antibiotics at various concentration ratios, synergistic or additive effects, or antagonism, as well as the action of each antibiotic alone.

Laboratory findings were reported to the clinician in charge of the patients suffering from Salmonella infections. In 17 patients combined therapy with chloramphenicol and tetracycline was not employed. The remaining 12 children, however, were treated with a combination of two synergistic or additive antibiotics as determined by the in vitro test.

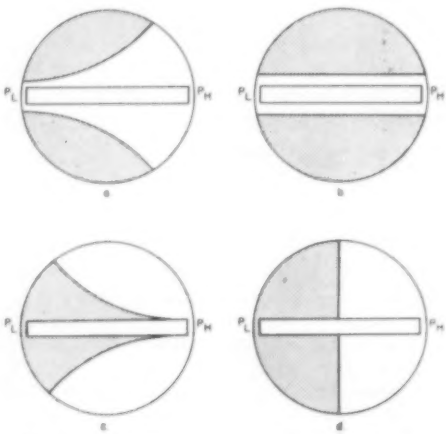


Fig. 2.—Patterns of bacterial growth on strip-gradient plates. (*a*) Synergistic or additive action. Note the symmetrical flaring zone of inhibition of growth in the plate from P_L to P_H; (*b*) growth inhibition only by antibiotic from strip; (*c*) antagonistic action of antibiotic from strip on growth-inhibition of plate antibiotic; (*d*) growth-inhibition only by primary antibiotic (in plate).

*Supplied as diagnostic antibiotic kits by Charles Pfizer & Company, Inc., Brooklyn.

Every animal in the rat colony, ill or well, was treated immediately with an antibiotic combination.

Strip-gradient investigations revealed that the combination of chloramphenicol with each of the three tetracycline antibiotics (chlortetracycline, oxytetracycline, and tetracycline) was additive or synergistic in inhibiting growth of the salmonellae tested. As a result of these in vitro studies, as well as other considerations discussed below, the drug combination employed in each instance consisted of chloramphenicol and tetracycline. Dosages varied; they are detailed for each patient in the accompanying appendix of case reports. Additional supportive therapy included the correction of electrolyte imbalance, anemia, and dehydration by the appropriate administration of blood, fluids, and diet.

Replica Strip-Gradient.[11,18]—Tetracycline and chloramphenicol are each bacteriostatic against salmonellae in concentrations commonly achieved by usual clinical dosage. To test whether or not these antibiotics were bactericidal when used in combination, the replica strip-gradient procedure (an adaptation of the Lederberg replica plating technique [18] to the strip-gradient method) was employed.

After 24-hour incubation of a strip-gradient plate, a surface imprint was taken on a sterile velvet pad and stamped onto the surface of a sterile blood agar base (Difco) plate free of antibiotics. This replica plate was read after overnight incubation at 37 C.

Absence of growth on any area of the original strip-gradient plate represented either inhibition or death of the organisms seeded onto this area. Subsequent growth on the corresponding area of the replica plate indicated survival and, hence, only bacteriostatic action of the combined antibiotics in the concentration ratios set for these areas on the strip-gradient plate. No growth on the corresponding area on replica plating denoted bactericidal action of the antibiotics.

Results

The results of antibiotic sensitivity studies carried out by a standard disc method on all Salmonella cultures from stock, human, or murine sources are listed in Tables 1 and 2. Chloramphenicol, chlortetracycline, oxytetracycline and tetracycline were uniformly

TABLE 1.—*Antibiotic Sensitivity Findings on Salmonella Cultures from Twenty-Nine Patients*†

Case	Type	Group	Antibiotic Discs ‡											
			Sm	Pn	Tc	Te	Au	Cl	Er	Mg	Ba	SmH$_2$	Ne	Poly
2	S. typhosa	D	S	SS	VS	VS	VS	VS	r*	r*	r*	SS	VS	—
4	S. typhimurium	B	S	R	VS	VS	VS	VS	r*	r*	r*	SS	VS	—
5	S. typhimurium	B	VS	R	S	S	S	VS	r*	r*	r*	S	VS	—
6	S. typhosa	D	VS	R	VS	VS	VS	VS	r*	r*	r*	SS	VS	—
7	S. sp. (Oranienberg) (initial culture)	C$_1$	VS	R	VS	VS	VS	VS	r*	r*	r*	S	VS	—
7	S. sp. (Oranienberg) (final culture)	C$_1$	S	R	r*	r*	r*	VS	R	r*	r*	S	VS	—
8	S. sp. (Oranienberg)	C$_1$	VS	R	VS	VS	VS	VS	r*	r*	r*	VS	VS	—
9	S. typhosa	D	VS	SS	VS	VS	VS	VS	r*	r*	r*	S	VS	—
10	S. typhosa	D	VS	SS	VS	VS	VS	VS	r*	r*	r*	ss*	VS	—
15	S. sp. (Oranienberg)	C$_1$	S	R	VS	VS	S	VS	r*	r*	r*	S	VS	—
16	S. typhimurium	B	S	R	VS	VS	S	VS	r*	r*	r*	S	S	—
18	S. sp. (Hartford)	C$_1$	VS	R	VS	S	VS	VS	R	r*	r*	S	VS	—
20	S. sp. (Oranienberg)	C$_1$	VS	r*	S	S	S	VS	r*	r*	r*	r**	—	—
22	S. typhimurium	B	r*	r*	S	S	S	VS	r*	r*	r*	r**	—	SS
23	S. typhimurium	B	VS	r*	VS	S	S	VS	r*	r*	r*	r**	—	—
24	S. typhimurium	B	S	R	VS	S	S	VS	r*	R	r*	S	—	SS
26	S. typhosa	D	S	R	VS	S	VS	VS	r*	r*	r*	SS	VS	S
27	S. typhimurium	B	VS	R	—	S	S	VS	r*	r*	r*	S	—	S
28	S. typhimurium	B	S	R	VS	S	S	VS	r*	r*	r*	SS	S	S
30	S. typhimurium	B	r*	R	S	S	S	VS	r*	r*	r*	—	S	S
31	S. sp. (Berta)	D	VS	R	VS	VS	VS	VS	r*	r*	r*	VS	VS	S
32	S. sp. (Oranienberg)	C$_1$	VS	R	VS	S	S	VS	r*	r*	r**	S	VS	S
33	S. sp. (Oranienberg)	C$_1$	S	R	S	S	S	VS	r*	r*	r**	S	VS	r*
34	S. sp. (Java)	D	VS	R	S	S	VS	VS	r*	r*	r**	r*	S	S
35	S. sp. (Java)	D	—	R	S	r*	S	S–VS	r*	r*	r**	r*	S	S
36	S. sp. (Oranienberg)	C$_1$	—	r*	VS	VS	VS	VS	r*	r*	r*	S	S	SS
37	S. typhimurium	B	—	R	S	S	S	VS	r*	r*	r*	SS	VS	SS
38	S. typhimurium	B	—	R	S	r*	r*	VS	r*	r*	r*	r*	VS	SS
39	S. sp. (München)	C$_2$	—	R	S	S	S	VS	r*	r*	—	S	S	SS
42	S. typhimurium	B	S	R	VS	VS	VS	VS	r*	r*	r*	S	VS	—

† Four patients (cases 27, 30, 31, and 36) were adults.

‡ Antibiotic discs and their concentrations (low, intermediate, and high): Sm, streptomycin (2 γ, 10 γ, and 100 γ); Pn, penicillin (2, 5, and 10 units); Tc, tetracycline (5 γ, 10 γ, and 30 γ); Te, oxytetracycline (5 γ, 10 γ, and 30 γ); Au, chlortetracycline (5 γ, 10 γ, and 30 γ); Cl, chloramphenicol (5 γ, 10 γ, and 30 γ); Er, erythromycin (2 γ, 5 γ, and 15 γ); Mg, carbomycin (2 γ, 5 γ, and 15 γ); Ba, bacitracin (2, 10, and 20 units); SmH$_2$, dihydrostreptomycin (2 γ, 10 γ, and 100 γ); Ne, neomycin (5 γ, 10 γ, and 30 γ); Poly, polymyxin B (5 γ, 10 γ, and 30 γ).

Abbreviations: VS, very sensitive, definite inhibition in low antibiotic disc concentration; S, sensitive, no inhibition by low antibiotic disc concentration, but inhibition by intermediate concentration; SS, slightly sensitive, inhibition only by high antibiotic disc concentration; R, resistant, no inhibition by high antibiotic disc concentration; r*, resistant, tested with low and intermediate antibiotic concentrations only; r **, resistant, tested with low antibiotic concentration only; ss **, slightly sensitive, tested with low antibiotic concentration only.

TABLE 2.—*Antibiotic Sensitivity Findings on Fifteen Stock Salmonella Cultures and One Salmonella Culture Isolated During Rat Colony-Epidemic*

Culture	Type	Group	Antibiotic Discs †												
			Sm	Pn	Tc	Te	Au	Cl	Er	Mg	Ba	SmH$_2$	Ne	Poly	Sulfa
S 323	S. sp. (Hartford)	C_1	S	SS	S	S	S	VS	R	R	R	S	S	S	R
S 48	S. sp. (Stanley)	B	S	R	S	S	S	VS	R	R	R	S	VS	S	R
S 307	S. sp. (Worthington)	F	S	SS	VS	VS	VS	VS	R	R	R	S	S	SS	R
S 328	S. sp. (Montevideo)	C_1	S	R	VS	S	VS	VS	R	R	R	S	VS	SS	R
S 115	S. sp. (Thompson)	C_1	S	R	VS	VS	S	VS	R	R	R	SS	S	SS	R
S 304	S. sp. (Berta)	D	S	SS	VS	VS	S	VS	R	R	R	S	VS	SS	R
S 301	S. sp. (Oranienberg)	C_1	S	SS	VS	S	S	VS	R	R	R	S	VS	SS	R
S 283	S. sp. (Java)	D	S	R	VS	S	S	VS	R	R	R	S	S	SS	R
S 50	S. sp. (Derby)	D	S	R	S	S	S	VS	R	R	R	SS	VS	SS	R
S 333	S. sp. (Miami)	D	S	R	S	S	VS	VS	R	R	R	S	S	SS	R
S 2	S. sp. (Newport)	C_1	S	R	S	S	S	VS	R	R	R	SS	S	SS	R
S 101	S. sp. (Chester)	B	S	R	S	S	S	VS	R	R	R	S	VS	SS	R
S 013	S. cholerasuis var. Kunzendorf	C_1	SS	R	VS	S	S	VS	R	R	R	SS	VS	S	R
S 336	S. anatis	E_1	S	SS	VS	S	VS	VS	R	R	R	SS	VS	SS	R
S 335	S. schottmülleri	B	S	SS	VS	S	S	VS	R	R	R	SS	VS	SS	R
Rat colony	S. typhimurium	B	S	R	VS	VS	VS	VS	R	R	R	S	VS	—	—

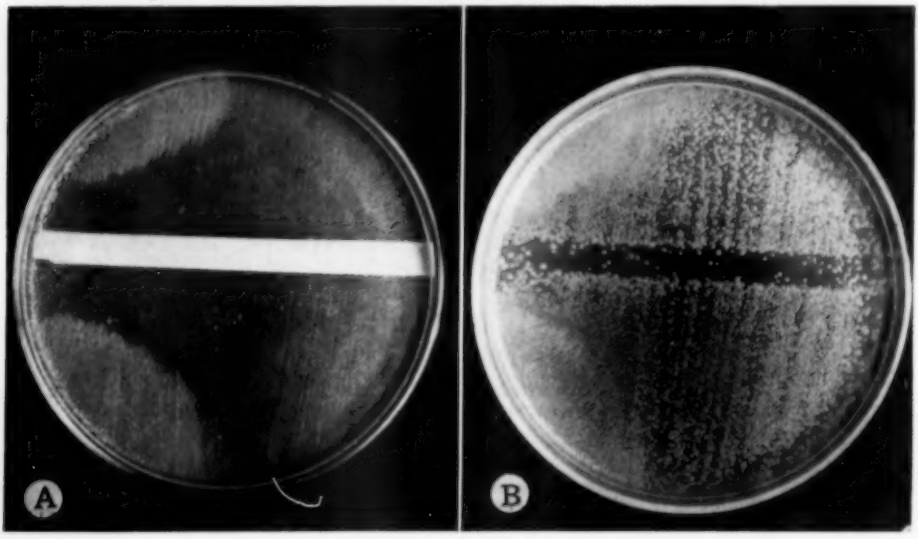
† Same concentrations and abbreviations as in Table 1; Sulfa, sulfadiazine (10 γ and 60 γ).

effective in inhibiting growth in vitro. Strip-gradient assays on all organisms demonstrated an additive or synergistic growth-inhibitory effect produced by the combination of chloramphenicol with any of the tetracycline antibiotics. Resistance to tetracycline was apparent in only one culture, isolated from a patient (Case 7) after he had received this medication to be taken at home; his pretherapeutic culture was sensitive to tetracycline.

Replica plates indicated that the additive or synergistic combination of chloramphenicol and tetracycline observed on strip-gradient plates was primarily bacteriostatic rather than bactericidal in action (Fig. 3).

Clinical Results.—Of the 29 patients from whose cultures salmonellae were recovered

Fig. 3.—Salmonella paratyphi B (culture No. S. 335). *A*, Strip-gradient plate showing additive or synergistic flare of inhibition of growth of S. paratyphi B by combination of chloramphenicol (maximum concentration of 5000γ per milliliter in strip) and tetracycline (maximum concentration of 20γ per milliliter in plate). *B*, replica plate of Figure 3*A* indicates that zones of growth inhibition on Figure 3*A* contain many viable organisms, which here grew out, in the absence of the antibiotics.



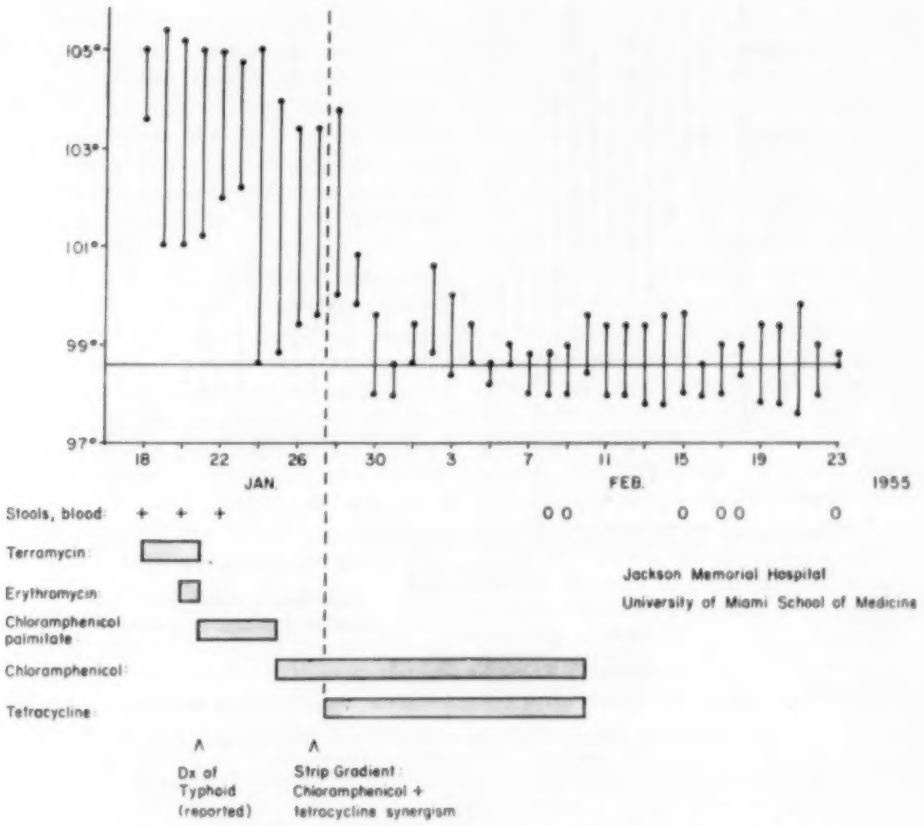


Fig. 4 (Case 2).—Course of S. typhosa infection in a 4-year-old Negro girl.

TABLE 3.—*Patients Treated for Typhoid Fever*

Case	Age, Yr.	Days of Illness Before Treatment	Nonexperimental Treatment *	Bacteriology After Nonexperimental Treatment *		Clinical Response to Nonexperimental Treatment	Duration of Experimental Treatment, Days	Bacteriology After Experimental Treatment *		Clinical Response to Experimental Treatment *	Comments
				Blood	Stool			Blood	Stool		
Experimental cases											
2	4	3	Te, Er+Te, Cl (6)	Not done	Not done	F	14	S	S	S	6 days of Cl without clinical response; clinical response ½ day after experimental treatment was started
26	7	8	Cl+Pn+ SmH_4 (1) Cl (8)	Not done	S (1 culture only)	F	9	Not done	S	S	9 days of Cl without clinical response; clinical response prompt and dramatic after experimental treatment was started
Control cases											
6	14	5	Cl (10)	Not done	Not Conclusive	S	..	..	..	..	Clinical response 3 days after treatment was started; stool cultures negative throughout; diagnosis and treatment dependent on rise in agglutination titer
9	16	21	Cl (19)	Not done	F	S	..	..	..	..	Clinical response 7 days after treatment was started
10	7	14	Cl (4), Cl+Cts (10)	Not done	Not conclusive	S	..	..	..	..	Clinical response immediate to Cl+Cts; blood culture positive on admission, but not repeated; stool cultures negative throughout illness

* Number of days in parentheses. S, satisfactory result; F, failure; Cts, cortisone.

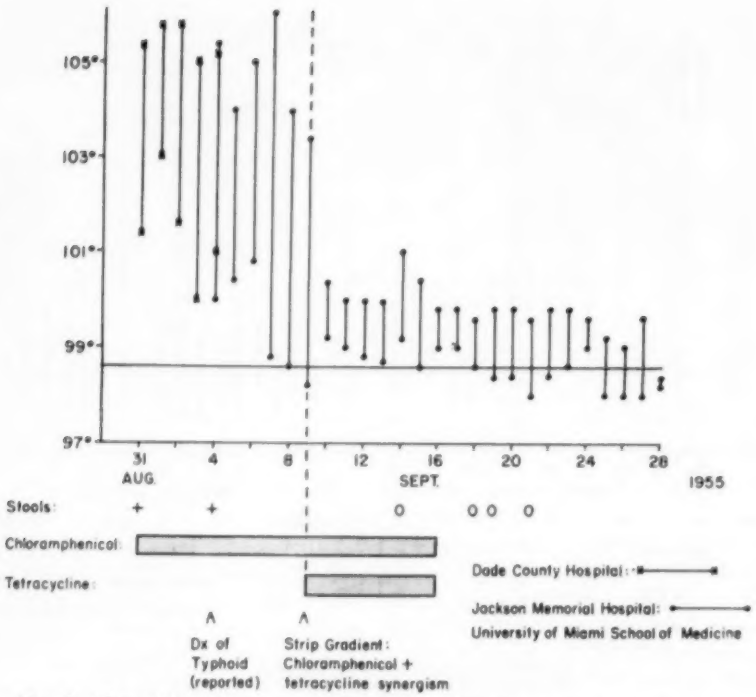


Fig. 5 (Case 26).—Course of S. typhosa infection in a 7-year-old Negro boy.

TABLE 4.—*Patients Treated for Salmonellosis (Other Than Typhoid Fever) with Combined Chloramphenicol-Tetracycline*

Case	Age	Days of Illness Before Treatment	Organism	Previous Treatment*	Clinical Response After Nonexperimental Treatment	Bacteriology After Nonexperimental Treatment (Stools)	Duration of Experimental Treatment, Days	Bacteriology After Experimental Treatment	Clinical Response to Experimental Treatment	Comments
Patients who received combined therapy without prior Cl										
15	7 mo.	14	S. sp. (Oranienberg)	Tc (4)	F	Not done	10	S	S	Clinical response in 2 days
20	8 wk.	14	S. sp. (Oranienberg)	0	..	..	12	S	S	Clinical response in 4 days
24	6 mo.	7	S. typhimurium	Tc (4) Tc (1)	S after Tc	Not done	9	F	S	Pneumonitis on adm.; x-ray clearing after experimental treatment; only 1 culture done after experimental treatment
34	13 days	2	S. sp. (Java)	Gn†+Pn (5) Gn (8)	F	S	5	..	S	Diarrhea persisted despite neg. stool cultures before experimental treatment; cleared after 3 days of combined treatment
38	14 mo.	2	S. typhimurium	Tc (3)	S	Not done	5	S	..	Experimental treatment started because of routine program
Patients who received combined therapy because of failure of Cl alone										
4	2 mo.	1	S. typhimurium	Tc (6) Cl (7) Neo (25)	S after Cl	F	6	Not done	..	Patient not available for follow-up
7	3½ mo.	5	S. sp. (Oranienberg)	Tc (5) Cl (15)	S after Cl	F	4	F	..	Patient not available for follow-up
8	1½ mo.	14	S. sp. (Oranienberg)	Tc (12) Cl (14)	S after Cl; recurrence in 3 wk.	F	5	Not done	S	Cl alone was readministered for 7 days immediately before combined treatment
16	21 mo.	14	S. typhimurium	Cl (13)	F	Not done	12	S	S	Clinical response after 4 days of experimental treatment

* Days in parentheses. † Gn, sulfisoxazole ("Gantrisin," Hoffman-La Roche, Inc.)

and studied by strip-gradient and replica procedures, 4 were adults and were excluded from this report. Fourteen pediatric patients did not receive combined chloramphenicol and tetracycline therapy. Eleven children did receive combined treatment with these antibiotics; two were suffering from typhoid fever and nine from other types of Salmonella infections.

Table 3 describes the results obtained in cases of typhoid fever. Two children (Cases 2 and 26, Figs. 4 and 5) received combined chloramphenicol and tetracycline because chloramphenicol alone failed to induce a satisfactory clinical response; both of these patients responded promptly to the combined medication. The three additional patients (Cases 6, 9, and 10) suffering from typhoid fever were treated with chloramphenicol alone (Cases 6 and 9) or chloramphenicol plus cortisone (Case 10) and responded satisfactorily.

Nine patients (Table 4) received combined chloramphenicol and tetracycline as treatment for Salmonella infections other than with S. typhosa. These children may be divided into two groups. Five patients had not received chloramphenicol prior to combined therapy. One of these (Case 20) had been given no previous antibiotics; he responded clinically and bacteriologically to combined medication. In two children (Cases 15 and 34) therapy had failed clinically (one on four days of tetracycline; one on combined sulfisoxazole (Gantrisin *) and penicillin); both had clinical recovery after combined chloramphenicol and tetracycline therapy. The pneumonitis of Case 24 cleared somewhat on short-term therapy with tetracycline followed by oxytetracycline but cleared radiologically only after combined chloramphenicol-tetracycline medication. The fifth child (Case 38) gave a satisfactory clinical response to a short course of tetracycline but was placed on combined therapy because of the experimental program in progress. After combined treatment, successive stool cultures from four of the five children in this series revealed no salmonellae; one of these patients (Case 34) was negative before insti-

*Hoffman—La Roche, Inc.

TABLE 5.—*Salmonella Cases in Which Combined Therapy Was Not Given*

Case	Age	Days of Illness Before Treatment	Organism	Antibiotic Therapy *	Bacteriological Results	Clinical Results	Comments
Patients who received no antibiotics							
18	2 yr.	4	S. sp. (Hartford)	None	(8)	F	Only 1 follow-up culture available; treatment with camphorated opium tincture cleared spontaneously
28	7 yr.	0	S. typhimurium	0	...	...	Diagnosis: nephrotic syndrome; organism found on routine culture; no symptoms
Patients who received antibiotics other than Cl							
22	8 mo.	5 hr.	S. typhimurium	Pn+Gn (1) Tc (6)	Not done	S	Bronchopneumonia and pyelonephritis; x-ray, partial resolution after 6 days of treatment, then discharged
23	2 mo.	2	S. typhimurium	Tc+Te (3)	Not done	F	Discharged as cured; recrudescence after 3 days; patient not available for follow-up
37	15 mo.	4	S. typhimurium	Tc (6)	Not done	F	Discharged to continue medication at home
39	1½ yr.	9½ mo.	S. sp. (München)	Gn (15)	Not reported	F	Recurrent periodic diarrhea episodes; patient not available for follow-up
Patients who received Cl treatment							
5	11 mo.	4	S. typhimurium	Te (6) Cl (14) Te (14) Neo (16)	S after Neo	S after Neo	Cl failed clinically and bacteriologically
32	4 mo.	2	S. sp. (Oranienberg)	Pn (1) Gn (7) Cl (8)	S	S after 1 day Cl	
33	3 mo.	2	S. typhimurium	Cl (10) Gn (5)	Not done	F	Diarrhea present on discharge; patient failed to keep clinic appointment
35	7 days	9	S. sp. (Java)	Gn+Bi (3) Gn (7) Cl (4) Cl+SmH, (7) Cl (7)	Not done	S after Cl+SmH,	
42	2 mo.	30	S. typhimurium	3 Sulf (6) Cl (11)	S after Cl	F	Experimental treatment prescribed at home; no follow-up available

* Days in parentheses.

tution of the paired antibiotic therapy. Case 24 was still a bacteriological failure after nine days of combined medication.

Two of the remaining four children received chloramphenicol and tetracycline because of clinical failure on chloramphenicol following tetracycline (Case 8) or on chloramphenicol alone (Case 16). Both of these children recovered when combined medication was administered. Combined treatment was given to two other children (Cases 4 and 7) who had responded clinically to chloramphenicol but who had continued to harbor salmonellae in their stools. One child (Case 7) continued to pass salmonellae after four days of combined therapy; no other follow-up data were available on any of these three patients.

Results in Rats.—Cultures of S. typhimurium were isolated from the lungs of animals in a rat colony at the time that four additional animals were ill with pulmonary disease and two were ill with diarrhea (see Appendix). Several animals had died previously in the same epidemic. The six sick rats, as well as all remaining members of the colony, were treated with combined chloramphenicol and tetracycline, with prompt and complete cure of the ill animals. No further cases developed. Several weeks later, the six rats that had been ill were killed and autopsied. No evidence of pulmonary or gastrointestinal disease was found.

Comment

Combined treatment of clinical salmonellosis with chloramphenicol and tetracycline in patients who had failed to respond adequately to standard antibiotic therapy resulted in prompt and uniform improvement in the subjective symptoms and objective signs of illness. The value of combined treatment was substantiated by the abrupt and complete interruption of a S. typhimurium outbreak in a rat colony. The efficacy of chloramphenicol-tetracycline treatment for salmonellosis awaits further evaluation in a larger series of patients treated with this combined medication, as compared with an adequate therapeutic control series.

This therapeutic use of tetracycline in addition to chloramphenicol was suggested by in vitro studies by the strip-gradient technique for the evaluation of combinations of antibiotics performed on salmonellae isolated from the above 11 patients, on strains recovered from 18 additional patients with salmonellosis, on 15 different types provided by the Florida State Board of Health, and on a strain isolated from the rat colony epidemic.

The combination of chloramphenicol and tetracycline was not the only one which appeared effective against salmonellae in vitro, as determined by the strip-gradient technique. The combination of chloramphenicol and each of the three tetracyclines consistently demonstrated additive or synergistic growth-inhibitory action in vitro against all the species and strains of salmonellae tested. Tetracycline rather than oxytetracycline or chlortetracycline was recommended for clinical trial because tetracycline is known to produce fewer side-effects [14,16-19,21-25] and gives high, prompt, maintained serum levels at ordinary dosage.[14,16-19,21-25]

Past experience with antibiotic sensitivity determinations has demonstrated that in vitro results can not be relied upon always in clinical trials. In the present study, in vitro and in vivo findings correlated very well.

As previously described,[7] the strip-gradient method has the following attributes: (*a*) It provides single-plate serial assay of bacterial sensitivity to growth-inhibitory action of a single antibiotic; (*b*) it enables the determination of the pattern of resistance of members of a bacterial culture in the presence of varying concentrations of a single antibiotic; (*c*) it is a simple, rapid technique for testing bacterial sensitivity to a pair of antibiotics, and (*d*) it presents graphically the synergistic or additive, indifferent, or antagonistic growth-inhibitory action of two antibiotics in combination at

various concentration ratios. Thus, this procedure offers a guide to early therapy and an index of drug sensitivity of organisms as they are isolated during the course of treatment. The strip-gradient technique has been utilized as a guide to therapy of patients suffering from other bacterial infections, e. g., those due to Pseudomonas, coagulase-positive Staphylococcus aureus, Brucella, and viridans Streptococcus. In each instance, though the infection was previously resistant to treatment with a single antibiotic, the combination suggested by our technique evoked a prompt and adequate therapeutic response.

Despite the indication of synergistic or additive effects demonstrated by the strip-gradient technique, the method falls short of differentiating bactericidal from merely bacteriostatic action of single or combined antibiotics. The replica strip-gradient procedure [11,12] was devised to give this additional information. By this new method, antibacterial effects of chloramphenicol and tetracycline, either alone or in combination, were found to be primarily bacteriostatic rather than bactericidal. These data confirm the report of Woodward et al.[26] that high concentrations (1000γ/ml.) of chloramphenicol are bacteriostatic rather than bactericidal against S. typhosa. We concur in the belief [2,26] that chloramphenicol only suppresses the growth of most of the infecting organisms and that recovery depends on the development of host defenses. The in vitro action of the combination of chloramphenicol and tetracycline in inhibiting, but not killing, salmonellae may account for failure of elimination of these organisms from stool cultures of patients treated with the antibiotic combination over too short a period of time to permit development of host defenses adequate to eradicate the infecting organisms. The replica strip-gradient plate results here reported have indicated that although the combination of chloramphenicol and tetracycline acting in vitro on various species of salmonellae exerts an additive or synergistic effect, this action is primarily bacteriostatic rather than bactericidal.

Why did combinations of chloramphenicol and tetracycline succeed clinically when chloramphenicol alone failed? We may speculate that the efficacy of the combination may be due to diffusion of tetracycline to some focus of infection in the host that is reached either not at all or only in subbacteriostatic concentration by chloramphenicol. Increased dosage of chloramphenicol alone might have accomplished the same clinical result, but the combination avoided the necessity for very high, potentially toxic, doses of chloramphenicol. Our in vitro findings (Tables 1 and 2) confirm previous reports [18,27-29] of the inhibitory action of tetracycline on various species and strains of salmonellae. Clinical trial of this drug alone in high doses (50-100 mg/kg/day, for 7-12 days) however, has given results in typhoid fever "inferior to those observed with chloramphenicol" [27]; another study has suggested that in the treatment of typhoid fever "tetracycline seems to be considerably less useful than chloramphenicol." [29]

Matteucci and co-workers [2] have indicated that "the total duration of [chloramphenicol] treatment should probably coincide with the accepted average duration of unmodified typhoid fever if the best results are to be obtained." We believe that, for eradication of the carrier state or prevention of development of recurrences, the combined antibiotics should be administered for a minimum of 14 days, until more data on length of required treatment for eradication of the carrier state become available. Such studies are now in progress.

Summary

Strip-gradient studies performed on 45 species and strains of salmonellae demonstrated the in vitro efficacy of combined use of chloramphenicol and tetracycline in inhibiting growth of these organisms. The 45 strains consisted of 29 isolates from stool or blood cultures from patients ill with Salmonella infections (including five patients

with typhoid fever), 1 isolate from a rat colony epidemic of pulmonary and gastrointestinal salmonellosis, and 15 stock strains of different groups and types of salmonellae.

Replica strip-gradient investigations indicated that the effects of the combined antibiotics were bacteriostatic rather than bactericidal.

These in vitro results were used as guides to therapy in 11 human patients (2 with typhoid fever and 9 with other types of salmonellosis), who had failed to respond adequately to prior medication with single antibiotics or combinations other than chloramphenicol and tetracycline. The two children with typhoid fever and four with other Salmonella infections were treated because of the persistence of clinical illness; all responded satisfactorily to combined medication with chloramphenicol and tetracycline. Two additional patients were treated with this combination of antibiotics because of failure of chloramphenicol alone, following medication with other antibiotics, to eradicate the organisms from their stools; inadequate follow-up data are available to evaluate combined therapy in these three cases. The remaining three patients received combined antibiotic medication because of the trial therapeutic regimen in progress, with satisfactory clinical results.

Tetracycline-chloramphenicol treatment of salmonellosis is discussed from the standpoint of correlations of in vitro observation with in vivo application. Though no conclusions can be drawn, because of the small number of patients actually treated, and because of the lack of a controlled series, we believe that our findings warrant further clinical trial of this antibiotic combination.

Appendix

Case 2 (Fig. 4).—A 4-year-old Negro girl, ill for three days, was admitted to Jackson Memorial Hospital, Miami, Fla., on Jan. 18, 1955. On admission, she had a temperature of 105.8 F; pulse rate, 140; albumin and acetone in the urine. Blood cell count showed 14,000 WBC, 51% segmented cells, 19% stab cells, 30% lymphocytes, 11 gm. hemoglobin per 100 cc., 3,940,000 RBC. X-ray of the chest revealed congestion in both lower lobes. Diplococcus pneumonia was found in the throat, and a tentative diagnosis of pneumonia was made. Three days later, the blood culture, taken on admission, revealed Group D Salmonella (S. typhosa). Blood cultures taken Jan. 20, 1955, and Jan. 22, 1955, also were positive. Agglutination titers were as follows: S. typhosa, O. antigen, 1:320; H antigen, 1:80; S. paratyphi A, 1:40; S. paratyphi B, Bacillus proteus Ox19, and Brucella abortus, 0; heterophile antigen, 1:28. A stool culture was negative for salmonellae. Before the diagnosis of typhoid fever was established, the patient was treated for pneumonia; she received oxytetracycline (75 mg. q. 6 h.) for one day (1/19/55), and, on the second day, because of persistent high temperature, erythromycin (75 mg. q. 6 h.) was added (Jan. 20, 1955). Later treatment, after the diagnosis of typhoid fever was made, consisted of chloramphenicol palmitate (14 cc. q. i. d., 125 mg/4 cc.) for four days (Jan. 22-25, 1955) and then chloramphenicol (250 mg. q. i. d.) for two days (Jan. 26 and 27, 1955). Failure to respond clinically was the reason for instituting combined antibiotic therapy (Jan. 28, 1955) with chloramphenicol (250 mg. q. i. d.) and tetracycline suspension (1.5 gm/2 fl. oz. [60 cc.], 1 teaspoonful [4.9 ml.] q. i. d.). Clinical response was dramatic. Therapy was continued for 14 days (until Feb. 10, 1955). Blood (Feb. 8, 1955), stool (Feb. 9, 15, 17, and 23, 1955) and urine (Feb. 18, 1955) cultures were negative, and the patient was discharged well, on Feb. 23, 1955.

Case 4.—A 2-month-old Negro girl was admitted to Jackson Memorial Hospital on Jan. 22, 1955, because of 8 to 10 loose stools during the preceding 24 hours. The infant was treated for accompanying dehydration. There was minimal febrile reaction. Blood cell count revealed 3,820,000 RBC, 12.1 gm. hemoglobin per 100 cc., 18,300 WBC, 3% juvenile forms, 27% stab cells, 17% segmented cells, 36% lymphocytes, 6% monocytes, 1% basophils. The urine was normal. Agglutination tests for the typhoid and paratyphoid antigens were negative. Stool culture taken on Jan. 24, 1955, was negative. Tetracycline (5 mg. q. 4 h.) was administered for one day (Jan. 22), followed by 25 mg. q. 6 h. until Jan. 28. Stools still contained blood and mucus, and later Group B Salmonella (S. typhimurium) was isolated from the stool taken on Feb. 4, reported on Feb. 10. The patient then received chloramphenicol (50 mg. q. 6 h.) for seven days (Feb. 10 to 17), with clinical recovery but with persistence of the organism in the stool (Feb. 21 and 25). A course (March 3 to 28) of neomycin (oral suspension, 60 mg. daily for 25 days) failed to rid the child of salmonellae (cultures positive on March 7, 11, 21, and 26 and April 1 and 2). A course of treat-

ment with chloramphenicol palmitate (60 mg. q. i. d.) plus tetracycline (60 mg. q. i. d.) then was begun (April 12). On April 13, the stool culture was still positive. Four days later (April 17) the child was discharged, to continue therapy for an additional 10 days. No follow-up was available, and so final evaluation of therapy cannot be made.

CASE 7.—A 3½-month-old Negro boy was admitted to Jackson Memorial Hospital on March 1, 1955, because of diarrhea (five or six stools per day) of five days' duration. The temperature remained normal throughout the entire period of observation. Blood cell count showed 3,000,000 RBC, 8.6 gm. hemoglobin per 100 cc., 11,000 WBC, 13% stab cells, 17% segmented cells, 70% lymphocytes. On admission, blood culture showed no growth. Stool cultures taken March 3, 4, and 5 revealed no salmonellae or chigellae. Oxytetracycline (25 mg. q. 6 h.) was administered for five days (March 2-7). Medication was discontinued then, and no further antibiotics were given, despite the persistence of diarrhea. Stools taken on March 15, 16, 17, and 18 yielded Salmonella Group C_1 (Salmonella sp. [Type Oranienberg]), between March 22 and April 8. Chloramphenicol (40 mg. q. 8 h.) was administered for nine days (March 22-31). Clinically, the child improved (diarrhea subsided), but stools remained positive for salmonellae (March 31). Chloramphenicol then was given for another six days (April 7-13), without clearing the stool cultures. Combined therapy with chloramphenicol and tetracycline (75 mg. b. i. d. of each) was administered for four days (April 14-18), but stools (April 20 and 22) were still positive. A week later, on April 25, the child was discharged, with instructions to the parents to recommence administration of the two antibiotics for a 10-day period. Ten days after discharge (May 5) follow-up stool cultures were again positive, and the Salmonella culture isolated now showed resistance to tetracycline, although the organism was still sensitive to chloramphenicol. No further follow-up studies were available.

CASE 8.—A 1½-month-old white girl was admitted to Jackson Memorial Hospital on Jan. 31, 1955, because of diarrhea and failure to gain weight since birth. Diarrhea subsided spontaneously, and no therapy was required. The child was afebrile. Weight gain was recorded. Diarrhea recurred 10 days later. A stool culture on Feb. 11 was negative. A stool taken Feb. 21 was reported positive for a Group C Salmonella (Salmonella sp. [Type Oranienberg]). Since there were other children in the diarrhea nursery at this time with the same organism, the possibility of a cross infection was considered. Tetracycline (35 mg. q. 6 h.) was administered to the child for 12 days (March 17-29), but a stool culture taken on April 1 was reported positive. A course of chloramphenicol palmitate (50 mg. q. 6 h.) was given for 14 days (April 2-15), and the infant was discharged on April 16. She was readmitted on May 8 because of recurrence of diarrhea. Blood cell count showed 3,450,000 RBC, 11.7 gm. hemoglobin per 100 cc., 11,400 WBC, 15% stab cells, 17% segmented cells, 65% lymphocytes, 3% monocytes. Stool cultures taken on May 10 yielded Salmonella sp. (Type Oranienberg) on May 16. Chloramphenicol palmitate (65 mg. q. i. d.) was begun on May 18. To this was added (May 25) tetracycline, pediatric drops (50 mg. q. 6 h.). Combined medication was given until May 30 and then discontinued. The child responded clinically with subsidence of diarrhea, but a stool culture (June 1) was positive for salmonellae. On June 6 treatment with chloramphenicol and tetracycline (50 mg. q. 6 h. of each) was resumed. The child was discharged on June 8, with instructions to the parents to continue administration of this medication for an additional 10 days. The patient was seen occasionally for a variety of illnesses at the outpatient clinic, until Sept. 24, 1955. There were no recurrences of diarrhea to that date, but no stool cultures were taken.

CASE 15.—A 7-month-old Negro boy was admitted to Jackson Memorial Hospital on April 20, 1955, because of a cold and cough of two weeks' duration, diarrhea for one week, vomiting, and dehydration. Blood cell count showed 3,800,000 RBC, 8.1 gm. hemoglobin per 100 cc., 10,400 WBC, 29% stab cells, 39% lymphocytes, 29% neutrophils, 3% monocytes. A Salmonella, Group C_1 (Salmonella sp. [Type Oranienberg]) was isolated from the stool taken on April 21. Treatment with tetracycline (50 mg. q. 8 h.) for four days (April 22-26) failed to effect a clinical cure. The infant then received chloramphenicol and tetracycline (100 mg. q. 6 h. of each) for 10 days (April 26 to May 6). During the patient's entire stay in the hospital, he remained afebrile. Clinical improvement was rapid, and follow-up stool cultures (May 7 and 10) were negative. He was discharged as well on May 11.

CASE 16.—A 21-month-old Negro boy was admitted to Jackson Memorial Hospital on April 19, 1955, because of cough and cold, with diarrhea, of two weeks' duration. Anorexia and vomiting had been present for two to three days before admission. Blood cell count showed 6,000,000 RBC, 12.5 gm. hemoglobin per 100 cc., 6900 WBC, 9% stab cells, 30% segmented cells, 49% lymphocytes, 10% monocytes, 2% eosinophils. Agglutination tests for typhoid and paratyphoid were negative. A stool culture taken on April 20 was negative. Three weeks after admission, a stool culture taken on April 23 yielded a Group B Salmonella (S.

typhimurium). Repeated stools showed, in addition, Ascaris, Giardia, and Hymenolepis nana infestations. Chloramphenicol (125 mg. q. 6 h.) was started April 23 and was administered for one day by mouth, then was given intravenously (50 mg. q. 6 h.) for three days; then oral dosage (125 mg. q. 6 h.) was reinstituted for nine days. At this time (May 5), because of persistent diarrhea, tetracycline (100 mg. q. i. d.) was added to the medication. After four days the diarrhea subsided. Antibiotics were discontinued after 12 days of combined treatment (May 16). Three successive stool cultures (May 18, 19, and 21) were negative for salmonellae, and the patient was discharged, well.

Case 20.—An 8-week-old Negro boy was admitted to Jackson Memorial Hospital on April 20, 1955, because of watery diarrhea of two weeks' duration. The child was afebrile. Blood cell count showed 2,750,000 RBC, 7.0 gm. hemoglobin per 100 cc., 15,800 WBC, 18% stab cells, 7% segmented cells, 70% lymphocytes, 4% monocytes, 1% eosinophils. After repeatedly negative stool cultures (April 21, 22, and 23) a stool culture taken on May 10 and reported on May 15 was reported positive for Salmonella Group C_1 (Salmonella sp. [Type Oranienberg]); this may have represented a possible cross infection from other children in the diarrhea nursery at the time. Therapy with chloramphenicol and tetracycline (31 mg. each, q. 6 h.) was begun (May 16) and continued for 12 days (until May 27). Diarrhea subsided after four days of combined treatment. Three successive follow-up stool cultures (May 27, 28, and 29) were negative for salmonellae. The infant was discharged on June 6, well.

Case 24.—A 6-month-old Negro boy was admitted to Jackson Memorial Hospital on June 24, 1955, with a mild upper respiratory infection of one week's duration. Vomiting and diarrhea had been present for one day. The white blood cell count was 5850. A Group B Salmonella (S. typhimurium) was isolated from the stool. Chest x-ray revealed the presence of bilateral basilar pneumonitis. Temperature reached 101.2 F. On admission, medication consisted of tetracycline (125 mg. t. i. d.). This was changed four days later to oxytetracycline (100 mg. i. v., t. i. d.). The following day the temperature had dropped to normal. The next day (June 30) therapy was altered to chloramphenicol palmitate (25 mg. q. 6 h.) with tetracycline, pediatric drops (70 mg. q. 6 h.) by mouth. Five days after the combined treatment was instituted, x-ray of the chest showed essential clearing, except for residual minimal pleural effusion. The antibiotics were discontinued after a total of nine days of this therapy, and the child was discharged from the hospital on July 13. A stool culture taken the day before discharge was still positive for salmonellae. No further follow-up was available, and this child was considered a possible Salmonella carrier.

Case 26 (Fig. 5).—A 7-year-old Negro boy was admitted to Dade County Hospital on Aug. 31, 1955, because of temperature of 105.4 F; pulse rate, 144; abdominal pains; vomiting, and chills. The boy had been ill for four days. Blood cell count showed 8 gm. hemoglobin per 100 cc., 27% hematocrit value, 9100 WBC, 56% stab cells, 37% segmented cells, 7% lymphocytes. An admission blood culture was reported positive for S. typhosa three days later. On admission the patient was given chloramphenicol (150 mg. q. i. d.), as well as procaine penicillin G (400,000 units, i. m., b. i. d.) and dihydrostreptomycin sulfate (0.5 gm., i. m., b. i. d.). On the following day the medication was changed to chloramphenicol (250 mg. q. 4 h.) alone, before the blood culture report was received. On Sept. 4, when the diagnosis of typhoid fever was established, the patient was transferred to Jackson Memorial Hospital, isolation ward. Medication consisted of chloramphenicol (250 mg. q. 4 h.). Three days later the dosage was increased to 500 mg. q. 4 h. Because of the continued high temperature, after two days (Sept. 9) tetracycline (250 mg. q. 4 h.) was added to the therapy. Clinical response was prompt and dramatic. Antibiotic therapy was discontinued after nine days (Sept. 17). Successive stool cultures (Sept. 14, 18, 19, and 21) were negative. Clinically, the boy was well, and he was discharged, well, on Sept. 28.

Case 34.—A Negro boy was born at a Broward County hospital on Nov. 8, 1955, after a 32-week gestation; birth weight was 3 lb. 13½ oz. Three days later he was transferred to Jackson Memorial Hospital for prematurity care. The infant failed to eat well, and 13 days after birth (Nov. 21) he began to have diarrhea with blood-tinged stools. Five days later (Nov. 26) he was given sulfisoxazole (Gantrisin*) (1.25 cc. q. 6 h.) and procaine penicillin G (100,000 units b. i. d.). Penicillin was discontinued after five days, but sulfisoxazole was continued. Stool cultures taken Nov. 26 and 27 yielded Salmonella Group D (Salmonella sp. [Type Java]) on Dec. 6. Sulfisoxazole administration was discontinued on Dec. 8. Mucus and blood started on Nov. 21 and continued to be present in the stools until Dec. 25. Chloramphenicol (75 mg. q. 6 h.) and tetracycline (40 mg. q. 6 h.) were given for five days (Dec. 22-27). After the combined medication had been started, stool cultures taken previously were reported negative. Therapy was discontinued, and the child was discharged on Dec. 27.

Case 38.—A 14-month-old Negro boy was admitted to Jackson Memorial Hospital on Nov. 3,

* Hoffman-La Roche, Inc.

1955, because of bloody diarrhea (30 stools in 24 hours) and dehydration. Blood cell count showed 4,580,000 RBC, 7.66 gm. hemoglobin per 100 cc., 6000 WBC, 3% stab cells, 33% segmented cells, 56% lymphocytes, 8% eosinophils. Tetracycline syrup (125 mg. q. 6 h.) was prescribed. The diarrhea subsided completely on the following day. Salmonella Group B (S. typhimurium) was recovered three days after admission (Nov. 6), and medication was altered to chloramphenicol (50 mg. per kilogram per 24 hours), together with tetracycline syrup (50 mg. per kilogram). Antibiotics were discontinued after five days (Nov. 11), when the patient appeared clinically well and after two follow-up stool cultures (Nov. 8 and 11) had been reported negative. The child was discharged on Nov. 17 for return to the clinic. He was never brought, and so no further follow-up studies were available.

Rat Colony Epidemic.—A number of rats in a large colony being used for nutritional studies had died and six were ill at the time S. typhimurium (Group B) was recovered from a pulmonary abscess of the right lower lobe of one autopsied animal. Four rats had pulmonary abscesses; two had diarrhea. Because of the danger of loss of the entire colony, each animal received an intramuscular injection of chloramphenicol (75 mg. per kilogram) and tetracycline (35 mg. per kilogram) daily for three days. All animals remained well. The six sick rats recovered but were autopsied at a later date. No evidence of salmonellosis was found in these six animals or any other rat in the entire colony.

Miss Janet Guadagno gave technical assistance.

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Premature and Full-Term Infants

A Comparison of Their Maternal Histories

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The obstetric records of the mothers of all premature infants who were born at the Elizabeth Steel Magee Hospital during 1949 have been abstracted and analyzed. Obstetric records of the mothers of a control series of full-term babies have been similarly studied, and the two sets of data have been compared in an attempt to learn more about the etiology of premature births.

There were 386 premature infants among a total of 4602 deliveries, a total prematurity rate of 8.4%. Because of multiple births, these babies were the result of only 364 pregnancies. Their birth weights ranged from 400 through 2500 gm.

There were 338 full-term infants in the control series, 3 of whom were stillborn, 2 of whom died under one week of age, and 2 of whom were twins. They were chosen from a complete dated card file of all mothers who delivered live- and stillborn infants during 1949. Cards which showed babies born nearest to the times of birth of the corresponding premature infants were chosen. When a card drawn from the file recorded the birth of a premature infant, this card was rejected, and no substitution was made. There were 27 such cards, and, because of them, and the 2 twins, there are 338 control babies.

All data concerning each infant were transcribed onto an individual card for that infant. In the study series there were thus 386 cards, which represented 386 premature infants, but, because of multiple births, there were only 364 mothers. The cards were then sorted according to various infant categories, such as birth weight and sex. For simplicity in analysis, they were also sorted according to various maternal categories, such as toxemia or bleeding during pregnancy. Because the 386 cards represented, in fact, only 364 mothers, an error in the calculated incidence of certain maternal (and paternal) attributes has been introduced. It is felt that this error is slight. Numbers are too small for validation by detailed statistical analysis, and this has not been attempted. However, standard errors of differences between percentages were calculated, and the difference between two percentages is not discussed in this paper as probably meaningful unless it is greater than two times its standard error. Maternal Rh factors and congenital anomalies in the infants were not recorded with sufficient completeness to warrant discussion here.

Among the 338 control infants, 62, or 18.3%, were Negro; among the total of 4602 births, 897, or 19.4%, of the babies were Negro. Among the 386 study infants, 126, or 32.6%, were Negro. Thus, the white and Negro prematurity rates were 7.0% and 14.0%, respectively. Prematurity in white and Negro babies has been similarly defined—a birth weight of 400 through 2500 gm. Data concerning white and Negro infants, however, have been analyzed separately in both the control and study series.

A. Birth Weight Distribution and Mortality of Premature Infants

Table 1 lists the birth weight distribution excluding stillbirths and the mortality of the white and Negro premature infants as recorded in the hospital records. (An infant is listed as dead if the death occurred before he left the hospital; thus, mortality as used here implies neonatal mortality.) It also lists the weight distribution including stillbirths.

There is no great racial difference in weight distribution, and mortality increases for both races as weight decreases, as is well known. Mortality seems higher for white (11.3%) than for Negro (6.5%) infants, and there is a higher percentage of white still-

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TABLE 1.—*Weight Distribution and Mortality* of Premature Infants*

Weight Gm.	Excluding Stillbirths				Including Stillbirths		
	Babies, No.	Distribution, %	Deaths		Stillbirths, No.	Total Babies, No.	Distribution, %
			No.	%			
White infants							
1,000 or less	4	2.0	4	100.0	28	32	12.3
1,001–1,500	14	6.9	7	50.0	13	27	10.4
1,501–2,000	39	19.1	7	17.9	9	48	18.5
2,001–2,500	147	72.1	5	3.4	6	153	58.9
Total	204	100.	23	11.3	56	260	100.
Negro infants							
1,000 or less	1	0.9	1	100.0	13	14	11.1
1,001–1,500	11	10.2	3	27.2	1	12	9.5
1,501–2,000	15	13.9	3	20.0	3	18	14.3
2,001–2,500	81	75.0	0	0	1	82	65.0
Total	108	100.	7	6.5	18	126	99.

* Fifty-six, or 21.6% of all white premature infants were stillborn. Eighteen, or 14.3% of all Negro premature infants were stillborn

births (21.6% as compared with 14.3%). Numbers are too small for detailed analysis, however, and the differences here are not significant. It is apparent that stillbirths are an important complication of prematurity in both races.

B. Incidence of Factors That May Cause Prematurity

Tables 2A and 2B list the incidence of various factors that may cause prematurity. Study infants (including stillbirths and neonatal deaths) are grouped according to birth weight (in grams), and, in addition, the premature stillbirths and neonatal deaths are listed separately. When a maternal history showed two or more factors, it has been listed here as "multiple factors." As a result, subsequent figures for specific items to be discussed below, such as syphilis or toxemia, will differ from those of these Tables.

No abnormalities are reported for 50.4% of white and for 43.7% of Negro premature infants. Under 2001 gm., however, no abnormalities are reported for only 35.5% and 18.2% of white and Negro infants. Expressed differently, 71.0% of white premature infants with no reported abnormalities weighed over 2000 gm., as compared with 46.5% of white premature infants with reported abnormalities; 85.5% of Negro premature infants with no reported abnormalities weighed over 2000 gm., as compared with 49.3% of Negro premature infants with reported abnormalities. Furthermore, for premature stillbirths and neonatal deaths the percentages with no reported abnormalities are only 35.5% and 28.0% for white and Negro infants. The listed factors thus appear to be more frequently associated in this series with the smallest premature infants and with those who died.

TABLE 2A.—*Incidence of Factors That May Cause White Prematurity*

	White Study Infants						White Control Infants		Stillbirths and Neonatal Deaths	
	1,000 Gm. or Less	1001–1,500 Gm.	1,501–2,000 Gm.	2,001–2,500 Gm.	All Infants	% of Total	All Infants	% of Total	No.	% of Total
Multiple births	3	4	6	13	26	10.0	1	0.4	5	6.3
Placenta previa	0	4	0	2	6	2.3	2	0.7	3	3.8
Premature separation	5	1	8	6	20	7.7	1	0.4	12	15.2
Toxemia	0	1	4	9	14	5.4	11	4.0	4	5.1
Syphilis	0	0	1	2	3	1.2	2	0.7	1	1.3
Chronic disease *	0	0	0	2	2	0.8	7	2.5	0	0
Uterine anomalies	0	0	0	1	1	0.4	3	1.1	0	0
Two or mores †	10	0	3	11	24	9.2	18	6.5	13	16.5
Multiple factors ‡	4	7	8	14	33	12.7	0	0	13	16.5
No reported abnormality	10	10	18	93	131	50.4	231	83.8	28	35.5
Total infants	32	27	48	153	260	100.	276	100.	79	100.
No reported abnormality, %	31.2	37.0	37.5	60.7		50.4		83.8		35.5

*Defined later in text
† Two or more abortions, stillbirths, prematures, or neonatal deaths.
‡ Two or more of the listed factors previous or subsequent to present pregnancy.

TABLE 2B.—*Incidence of Factors That May Cause Negro Prematurity*

	Negro Study Infants						Negro Control Infants		Stillbirths and Neonatal Deaths	
	1,000 Gm. or Less	1,001–1,500 Gm.	1,501–2,000 Gm.	2,001–2,500 Gm.	All Infants	% of Total	All Infants	% of Total	No.	% of Total
Multiple births	0	2	1	2	5	4.0	1	1.6	0	0
Placenta previa	0	0	0	1	1	0.8	0	0	0	0
Premature separation	1	1	1	2	5	4.0	1	1.6	2	8.0
Toxemia	1	1	1	4	7	5.6	3	4.8	1	4.0
Syphilis	2	0	2	5	9	7.1	4	6.5	3	12.0
Chronic disease *	1	0	1	0	2	1.6	0	0	1	4.0
Uterine anomalies	0	0	0	0	0	0	0	0	0	0
Two or mores †	2	3	3	7	15	11.9	4	6.5	4	16.0
Multiple factors ‡	3	2	8	14	27	21.4	6	9.7	7	28.0
No reported abnormality	4	3	1	47	55	43.7	43	69.4	7	28.0
Total infants	14	12	18	82	126	100.	62	100.	25	100.
No reported abnormality, %	28.6	25.0	5.6	57.3		43.7		69.4		28.0

* Defined later in text.
† Two or more abortions, stillbirths, prematures, or neonatal deaths.
‡ Two or more of the listed factors previous or subsequent to present pregnancy.

C. Sex Distribution

Of 251 white premature infants 139 (55.4%) were female. Of 119 Negro premature infants 62 (52.1%) were female. In the control series, 122 of 276 (44.2%) white infants and 27 of 61 (44.3%) Negro infants were female. This female excess in the study series probably reflects the fact that female infants, in general, have an average lower birth weight.

D. Month of Birth

Birth dates of white and Negro premature infants in this series showed no marked seasonal trend.

E. Illegitimacy

Table 3 tabulates illegitimacy. For the purpose of this Table, an infant was considered illegitimate if the mother was not married, if she was separated from her husband, or if her husband was not the infant's father.

Table 3 shows that illegitimacy is not a problem for the white premature infants in this series, and its incidence does not differ from that among the white full-term infants. Among all the Negro premature infants, however, the incidence of illegitimacy is high (34.1%), even when compared with the high incidence among Negro full-term infants (16.1%). Furthermore, it is highest (43.7%) among Negro babies born prematurely without known cause.

The significance of the high rate in Negroes in not clear. It may reflect attempts at abortion, with resultant damage to but not death of the fetus, who is subsequently born prematurely. It may reflect a socioeconomic problem, with its implications of poor diet and prenatal care, especially since the most strikingly high incidence of illegitimacy is among Negro infants whose prematurity is unexplained. In any event, it appears that illegitimacy is an important problem for Negro premature infants in this series, especially for those born prematurely without known cause.

TABLE 3.—*Illegitimacy*

	White Infants			Negro Infants		
	Total No.	Illegitimate		Total No.	Illegitimate	
		No.	%		No.	%
Study Group						
Total	269	5	1.9	126	43	34.1
"No cause"*	131	3	2.3	55	24	43.7
"Cause"†	129	2	1.5	71	19	26.8
Control Group	276	4	1.4	62	10	16.1

* Listed under No Reported Abnormality in Tables 2A and 2B.
† Listed among possible causal factors in Tables 2A and 2B.

F. Length of Labor

Length of labor in hours is shown in Table 4. The percentage distribution is comparable for white and Negro premature infants and for white full-term infants. The percentage distribution for Negro full-term infants is altered because of the large proportion of long labors. It would seem that premature infants in this series experienced approximately the same number of labor hours as full-term infants.

TABLE 4.—*Length of Labor (Cesarean Sections Excluded)*

Hr. of Labor	White Infants				Negro Infants			
	Study Group		Control Group		Study Group		Control Group	
	No.	%	No.	%	No.	%	No.	%
0-2	16	7.6	16	6.4	8	7.3	2	3.3
3-5	57	27.2	64	25.8	29	26.6	12	19.7
6-10	76	36.4	91	36.6	38	34.8	16	26.2
11-15	33	15.8	40	16.1	18	16.5	16	26.2
16-20	16	7.4	23	9.3	8	7.3	4	6.6
21+	12	5.7	14	5.6	8	7.3	11	18.0
Total	209	100.	248	99.	109	99.	61	100.

G. Cesarean Sections

Among 260 white premature infants 19 (7.3%) were delivered by cesarean section; valid reasons for surgical interference existed in all cases. For 276 white full-term infants the incidence was 18 (6.5%); valid reasons for surgical interference were recorded for 16 cases. Among 126 Negro premature infants 7 (5.6%) were delivered by cesarean section; 6 of these sections were performed for stated, valid reasons. For 62 Negro full-term infants the incidence was 1 (1.6%); this was indicated. Unwarranted cesarean section, in this series, is not important in the etiology of prematurity.

H. Maternal Syphilis

Among 236 white premature infants there were three instances (1.3%) of positive serologic tests for maternal syphilis, as compared with two (0.8%) among 259 white full-term infants. Among 119 Negro premature infants there were 21 (17.6%) positive maternal tests, as compared with 6 (10.0%) among 60 Negro full-term infants. Syphilis is not important in the etiology of white prematurity in this series. For Negroes, however, although the incidence is not notably higher among premature than among full-term infants, it appears to remain an important problem in this series.

I. Chronic Maternal Disease

Chronic maternal disease (tuberculosis, diabetes, heart disease, chronic infections except syphilis, fibroids, anomalies of reproductive tract) was recorded for 15 (5.8%) of the mothers of 260 white premature infants, as compared with 10 (3.6%) of the mothers of 276 white full-term infants. Among Negroes the figures were 5 (4.0%) of 126 and 3 (4.8%) of 62, respectively. In this series chronic maternal disease does not seem important in the etiology of prematurity.

J. Toxemia

Toxemia (noted on the chart by the obstetrician as toxemia, preeclampsia, eclampsia, or hypertension with albuminuria) was recorded for 31 (11.9%) of the mothers of 260 white premature infants, as compared with 11 (4.0%) of the mothers of 276 white full-term infants. Among Negroes the figures were 22 (17.5%) of 126 and 6 (9.7%) of 62, respectively. Toxemia, in this series, seems significant in the etiology of white and probably of Negro prematurity.

K. Bleeding During Pregnancy

Bleeding during pregnancy is here defined as one or more episodes of vaginal bleeding which were recorded on the chart but not diagnosed as placenta previa or premature separation of the placenta. It was noted for 28 (10.8%) of the mothers of 260 white premature infants, and 23 of these episodes occurred during the first four months of pregnancy. Among the mothers of 276 white full-term infants it was noted in only two (0.7%). Although this latter percentage seems low and may reflect poor recording, these data suggest that vaginal bleeding, early in pregnancy, is associated in this series with a higher incidence of white premature births.

Among the mothers of 126 Negro premature infants only three (2.4%) had such

bleeding noted, and among the mothers of 62 Negro full-term infants, only one (1.6%). These percentages are so low that poor recording is suspected. When viewed with the knowledge, however, that the incidence of placental accidents is lower among Negro mothers of premature infants than it is among similar white mothers (see below), they suggest that placentation difficulties in this series are more important in the etiology of white than of Negro prematurity.

L. Placental Accidents

Among the mothers of 260 white premature infants 12 (4.6%) suffered from placenta previa and 31 (11.9%), from premature separation of the placenta. Among the mothers of 276 white full-term infants the figures were two and one, or a combined incidence of only 1.9%. Among the mothers of 126 Negro premature infants three (2.4%) suffered from placenta previa and six (4.8%), from premature separation of the placenta. Among the mothers of 62 Negro full-term infants, the figures were one and one, or a combined incidence of 3.2%. Placentation difficulties, especially premature separation, appear important in the etiology of white prematurity in this series.

M. History of Full-Term Stillbirths and Neonatal Deaths

When the hospital records showed a full-term baby stillborn or dying in the neonatal period born to a mother either previous to or up through five years subsequent to the birth of her baby in the present series, this fact was noted. The data are recorded in Table 5 and, in general, of course, do not include subsequent babies who may have been born to these mothers in other hospitals. This Table shows that the white and Negro premature infants did not have more previous and subsequent full-term stillborn siblings than did the control full-term infants. Negro premature infants had a slightly higher percentage of previous and subsequent full-term siblings dying in the neonatal period than did their controls, but numbers here are too small for analysis; percentages for white and premature infants and their controls do not differ significantly. It would seem, from this series, that premature infants are not more likely to have previous and subsequent full-term stillborn siblings or full-term siblings dying in the neonatal period.

N. Previous and Subsequent Abortions

When the hospital records showed that a mother had had a spontaneous abortion, either previous to or up through five years subsequent to the birth of her baby in the present series, this fact was noted. The data are recorded in Table 5. Again, it should be remembered that subsequent abortions in other hospitals are generally not included.

This Table shows that white premature infants had more previous and subsequent abortive siblings than white full-term infants. On the other hand, the incidence of abortive siblings among Negro premature and full-term infants is about the same. These data suggest that mothers of white premature infants in this series have a propensity for abortion.

TABLE 5.—*Previous and Subsequent Full-Term Stillbirths and Neonatal Deaths, Abortions, and Premature Births*

	White Infants				Negro Infants			
	Study Group (260)*		Control Group (276)		Study Group (126)		Control Group (62)	
	No.	%	No.	%	No.	%	No.	%
Stillbirths	6	2.3	7	2.5	7	5.6	3	4.8
Neonatal deaths	5	1.9	4	1.4	9	7.1	2	3.2
Abortions	85	32.6	52	18.8	41	32.5	17	27.4
Premature births	61	23.4	17	6.2	79	62.7	12	19.4

* Number of infants in each group is given in parentheses.

TABLE 6.—*Paternal Age*

Paternal Age, Yr.	White Infants				Negro Infants			
	Study Group		Control Group		Study Group		Control Group	
	No.	%	No.	%	No.	%	No.	%
15–25	51	20.2	65	23.8	37	32.2	24	40.0
26–35	141	55.7	153	56.0	49	42.6	28	46.6
36+	61	24.1	55	20.1	29	25.2	8	13.3
Total	253	100.	273	99.	115	100.	60	99.

O. Previous and Subsequent Premature Births

When the hospital records showed that a mother had had a premature infant previous to or up through five years subsequent to the birth of her baby in the present series, this fact was noted. The data are recorded in Table 5. Remember, again, that subsequent premature births in other hospitals are generally not included.

This Table shows that both white and Negro premature infants had a greater incidence of premature siblings than did their controls in this series. The incidence of premature siblings for both premature and full-term Negro infants is much higher than it is for the white infants.

If one recalls that bleeding during pregnancy, placental accidents, and abortions are commoner among mothers of white premature infants than among mothers of Negro premature infants, one might suggest that white mothers are prone to lose their babies earlier in pregnancy, as abortions, and Negro mothers are prone to carry them longer and deliver them alive, but prematurely. Thus, although much has been written about the problem of prematurity in the Negro race (as noted earlier, its incidence in this series is twice as great as in the white race), it may be that the problem in the white race is statistically obscured because the ultimate in prematurity is classified as abortion.

P. Paternal Age

Table 6 shows that fathers of Negro premature infants in this series tend to be older than fathers of Negro full-term infants. This may well be due to the fact that the mothers of Negro premature infants in this series tend to be older (see below). Ages of fathers of white premature and full-term infants do not differ greatly.

Q. Maternal Age

Ranges of maternal ages are shown in Table 7. In this Table, and hereafter, "no cause" refers to infants who were grouped under "no reported abnormality" and "cause" refers to infants who were grouped under various factors in Tables 2A and 2B.

Mothers of the total group of white premature infants appear to be slightly older (65.4% over 25 years) than mothers of white full-term infants (57.6% over 25 years). However, when the white premature

TABLE 7.—*Maternal Age*

Maternal Age, Yr.	Study Group						Control Group Infants	
	Total Infants		"No Cause" Infants		"Cause" Infants			
	No.	%	No.	%	No.	%	No.	%
White Mothers								
15–20	23	8.8	14	10.7	9	6.9	21	7.6
21–25	67	25.8	37	28.2	30	23.2	96	34.8
26–30	88	33.8	45	34.4	43	33.4	85	30.8
31–35	60	23.1	23	17.6	37	28.6	51	18.5
>35	22	8.5	12	9.2	10	7.8	23	8.3
Total	260	100.	131	100.	129	99.	276	100.
Negro mothers								
15–20	49	38.9	31	56.3	18	25.3	28	45.2
21–25	27	21.4	12	21.8	15	21.2	17	27.4
26–30	21	16.7	8	14.5	13	18.3	10	16.1
31–35	17	13.5	2	3.7	15	21.2	2	3.2
>35	12	9.5	2	3.7	10	14.1	5	8.1
Total	126	100.	55	100.	71	100.	62	100.

infants are grouped as "no cause" and "cause" it is apparent that it is the mothers of "cause" babies who are older (69.8% over 25 years) and mothers of "no cause" babies are comparable in age to the control mothers (61.2% over 25 years).

Mothers of the total group of Negro premature infants likewise appear to be slightly older (39.7% over 25 years) than mothers of Negro full-term infants (27.4% over 25 years), even though both groups are younger than the comparable white mothers. Here, again, it is apparent that it is the mothers of "cause" babies who are older (53.6% over 25 years) and mothers of "no cause" babies are comparable in age to the control mothers (21.9% over 25 years).

It is realized that it takes time for mothers to accumulate certain of the "causal" factors, notably that of "two or mores" (Tables 2A and 2B) and thus these mothers might automatically tend to be older. However, if the 24 white and 15 Negro "two or mores" babies are taken from the "cause" groups and added to the "no cause" groups of the two races, the percentages of mothers over 25 years of white and Negro "cause" babies become 69.4% and 57.1%, respectively; the percentages of mothers over 25 years of white and Negro "no cause" babies become 62.5% and 25.7%, respectively. These percentages do not differ significantly from those of the original groupings.

Table 7 thus suggests that it is the older mothers, especially Negroes, who are prone to bear infants whose prematurity may be explained by various factors (Tables 2A and 2B). It has been shown in a preceding section that these infants as a group are smaller and more of them die. It would seem, then, that advanced maternal age is of significance in the problem of prematurity.

R. Gravidity

Gravidity is shown in Table 8. Mothers of the total group of white premature infants appear to have had as many pregnancies as mothers of white full-term infants (study group, 62.3% multigravidas; control group, 62.2% multigravidas). Mothers of "cause" babies may have had more pregnancies (67.4% multigravidas) than mothers of "no cause" babies (57.3% multigravidas), but the difference is probably not significant here.

Mothers of the total group of Negro premature infants likewise appear to have had as many pregnancies as mothers of Negro full-term infants (study group, 71.4% multigravidas; control group, 69.3% multigravidas). Here, however, mothers of "cause" babies seem to have had more pregnancies (81.6% multigravidas) than mothers of "no cause" babies (58.1% multigravidas), but they have not had significantly more pregnancies than the control mothers. Furthermore, the greater incidence of pregnancies among the mothers of the Negro "cause" babies is explained, in part, by the fact that the "two or mores" (Tables 2A and 2B) are included in this group.

These data suggest that advanced maternal age, per se, and not greater number of pregnancies, is of significance in the problem of prematurity.

TABLE 8.—*Gravidity*

	Study Group							
	Total Infants		"No Cause" Infants		"Cause" Infants		Control Group Infants	
	No.	%	No.	%	No.	%	No.	%
White mothers								
Primigravidas	98	37.7	56	42.7	42	32.5	104	37.8
Secundigravidas	77	29.6	46	35.1	31	24.0	86	31.1
Multigravidas	85	32.7	29	22.2	56	43.4	86	31.1
Total	260	100.	131	100.	129	99.	276	100.
Negro mothers								
Primigravidas	36	28.6	23	41.8	13	18.3	19	30.7
Secundigravidas	34	27.0	18	32.8	16	22.5	16	25.8
Multigravidas	56	44.4	14	25.3	42	59.1	27	43.5
Total	126	100.	55	99.	71	99.	62	100.

TABLE 9.—*Maternal Hemoglobin Levels*

Hemoglobin, %	Study Group							
	Total Infants		"No Cause" Infants		"Cause" Infants		Control Group Infants	
	No.	%	No.	%	No.	%	No.	%
White mothers								
<66	17	10.7	6	9.0	11	12.1	14	9.1
66–75	57	36.1	24	35.8	33	36.3	59	38.3
76–85	71	44.9	32	47.7	39	42.8	67	43.5
>85	13	8.3	5	7.5	8	8.8	14	9.1
Total	158	100.	67	100.	91	100.	154	100.
Negro mothers								
<66	24	22.2	7	14.9	16	27.6	4	7.3
66–75	32	29.6	14	29.8	16	27.6	13	23.6
76–85	31	28.7	16	34.0	15	25.8	24	43.7
>85	21	19.5	10	21.3	11	19.0	14	25.4
Total	108	100.	47	100.	58	100.	55	100.

S. Maternal Hemoglobin Levels

Table 9 shows hemoglobin levels of mothers of the white premature and full-term babies. Levels were recorded for 60.8% of mothers of the premature infants and for 55.8% of mothers of the full-term infants. Most levels were determined during the third to fifth month of pregnancy. They were estimated by the Haden-Hauser method in most private and semiprivate patients and by the Tallquist method in all ward patients. The patients are not grouped according to these categories here, because levels of study and control mothers do not differ appreciably, as the Table shows. Maternal anemia does not seem to be associated with white prematurity in this series.

Table 9 also shows hemoglobin levels of mothers of the Negro premature and full-term babies. Levels were recorded for 85.8% of mothers of the premature infants and for 88.8% of mothers of the full-term babies. Most levels were determined during the third to fifth month of pregnancy. They were estimated by the Tallquist method (in all but three patients). The inaccuracy of this method is recognized, but it seems valid to compare study and control figures, on the assumption that the same degree of error is present in each group.

Table 9 shows that mothers of all the Negro premature infants seem to be more anemic (22.2% of them had hemoglobin levels below 66%) than the mothers of Negro full-term infants (7.3% of them had hemoglobin levels below 66%). However, the Table also shows that it is actually the mothers of the Negro "cause" babies who are more anemic than the controls. These mothers of "cause" babies include, of course, mothers with various troubles such as premature separation, which might cause anemia; however, hemoglobin determinations were generally done so early in pregnancy that these troubles do not explain the anemia.

The significance of the anemia is not clear, although it may be a reflection of poor socioeconomic conditions. It does seem, however, that maternal anemia in this series is associated with Negro "cause" prematurity.

T. Hospital Accommodations

Table 10 shows the ward status of white premature and full-term infants. The status of Negro infants is not given because almost all of these infants, both premature and full-term, were ward patients. The Table shows that a higher percentage of full-term than premature babies were ward patients

TABLE 10.—*White Hospital Accommodations*

	Study Group							
	Total Infants		"No Cause" Infants		"Cause" Infants		Control Group Infants	
	No.	%	No.	%	No.	%	No.	%
Private	54	20.8	24	18.3	30	23.2	76	27.5
Semiprivate	172	66.1	86	65.6	86	66.7	125	45.3
Ward	34	13.1	21	16.1	13	10.1	75	27.2
Total	260	100.	131	100.	129	100.	276	100.

TABLE 11.—*White Fathers' Work Status*

	Study Group						Control Group Infants	
	Total Infants		"No Cause" Infants		"Cause" Infants			
	No.	%	No.	%	No.	%	No.	%
Professional	39	15.0	18	13.8	21	16.5	31	11.2
Skilled	135	52.0	74	56.4	61	47.2	165	59.9
Unskilled	86	33.0	39	29.8	47	36.4	80	28.9
Total	260	100.	131	100.	129	100.	276	100.

(27.2% vs. 13.1%), but this fact is difficult to interpret. The high incidence of semiprivate premature infants (66.1%, vs. 45.3% for full-term infants) might suggest that mothers who would otherwise be ward patients obtain semiprivate accommodations when they enter labor prematurely. This suggestion may be further born out by the shift of the "cause" babies from ward to private status. Certainly, there is nothing in Table 10 to suggest that white prematurity is a socioeconomic problem in this series.

U. Father's Work Status

Table 11 shows the work status of fathers of white premature and full-term infants. The work status of fathers of Negro infants is not given because almost all of them were classified as unskilled. A status of "unskilled" was assigned when the father's occupation was obviously such, e. g., laborer; when his occupation was not stated, or when he was listed as unemployed. Table 11 reveals no real differences in paternal work status and offers nothing to suggest that white prematurity is a socioeconomic problem in this series.

Summary and Conclusions

The obstetric records of the mothers of 386 premature infants and of 338 full-term infants have been analyzed and the two sets of data have been compared in an attempt to learn more about the etiology of premature births. The following conclusions, concerning this study, can be drawn:

1. Prematurity rates for white and Negro births are 7.0% and 14.0%, respectively.

2. Birth weight distribution is similar for white and Negro premature infants.

3. Neonatal mortality and the incidence of stillbirths among white and Negro premature infants increase as birth weight decreases.

4. Stillbirths are an important complication of prematurity in both races.

5. Factors which might cause prematurity are more frequently associated with the smallest white and Negro premature infants and with those who die in the neonatal period.

6. There is a higher percentage of female white and Negro infants (54.3%) in the study series than in the control series (44.2%). This small female excess probably reflects the fact that female infants, in general, have an average lower birth weight.

7. Birth dates of white and Negro premature infants show no marked seasonal trend.

8. Illegitimacy is an important problem for Negro premature infants, especially for those born prematurely without known cause.

9. White and Negro premature infants experience approximately the same number of labor hours as do full-term infants.

10. Cesarean section is not important in the etiology of white and Negro prematurity.

11. Maternal syphilis is a problem for Negro premature and full-term infants (17.6% and 10.0%, respectively, positive serologic tests).

12. Chronic maternal disease does not seem important in the etiology of white and Negro prematurity.

13. Toxemia is significantly associated with white and probably with Negro prematurity.

14. Vaginal bleeding, early in pregnancy, is significantly associated with white prematurity.

15. Placentation difficulties, especially premature separation of the placenta, are significantly associated with white prematurity.

16. White and Negro premature infants have no increased incidence of full-term stillborn siblings or full-term siblings dying in the neonatal period.

17. Mothers of white premature infants show an increased incidence of spontaneous abortion.

18. White and, especially, Negro premature infants have an increased incidence of premature siblings.

19. The high incidence of vaginal bleeding, placental accidents, and spontaneous abortions among white mothers of premature infants and the high incidence of premature births among Negro mothers of premature infants seems important. It suggests that, although much has been written about the problem of prematurity in the Negro race (its incidence in this series was twice as great as in the white race), it may be that the problem in the white race is statistically obscured because the ultimate in prematurity is classified as abortion.

20. Fathers of Negro premature infants are older than the control fathers.

21. Mothers of white and Negro premature infants, when the prematurity is unexplained, are comparable in age to the control mothers. However, mothers of white and Negro premature infants, when the prematurity can be associated with a possible causal factor, are older than the control mothers. Because these infants whose prematurity is associated with a possible causal factor are, as a group, smaller and more of them die, it would seem that advanced maternal age is of significance in the problem of prematurity.

22. Mothers of white and Negro premature infants have not had more pregnancies than the control mothers. This suggests that maternal age, per se, and not greater number of pregnancies, is of significance in the problem of prematurity.

23. Maternal anemia is not associated with white prematurity or with unexplained Negro prematurity. However, mothers of Negro premature infants, when the prematurity can be associated with a possible causal factor, are more anemic than the control mothers.

24. Comparison of hospital accommodations for white premature and full-term infants does not suggest that white prematurity is a socioeconomic problem.

25. Comparison of the work status (professional, skilled, unskilled) of the fathers of white premature and full-term infants does not suggest that white prematurity is a socioeconomic problem.

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The Placental Transmission of Histoplasmosis Complement-Fixing Antibodies

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The placental transmission of immune antibodies to the newborn had been inferred by clinical observation for some years before Ehrlich proved its occurrence experimentally in 1892.[1] Since that time the transplacental passage of humoral antibodies has claimed the interest of many investigators who have made highly significant contributions to the basic knowledge of placental physiology and immunology. Practical results of their work have come from a clearer understanding of the previously observed neonatal immunity of many infants to infections which attacked them later in life. The relatively short duration of the newborn's passively acquired immunity has been well established by many of these investigations,[2-17] and a pattern of artificial immunization for infants has been devised as a result. The practice of actively immunizing expectant mothers in order to protect newborn infants was advocated even in the pre-Ehrlich era[18] and has been proposed anew in more recent times.[19-22]

The placental transfer of antibodies or antitoxins of a great variety of microbiological agents has been studied and reported. Several excellent reviews have been published.[23-25] It is not the intention here to present a comprehensive review of the voluminous literature on the subject but rather to arrange the data and references according to an accepted classification of the agent (Table 1) and to attempt to bring the studies up to date as a background for the present report. Only observations in humans will be considered, because considerable confusion developed in the past from attempts to apply to humans the results of studies of placental transmission in experimental animals.

From Table 1 it will be noted that studies on 21 microorganisms have been reported. So far as we know, reports of the placental transmission of antibodies to fungal agents have never appeared in the literature.* This is not surprising, since it is only within relatively recent years that the systemic mycoses have begun to excite widespread interest, largely due to the increasingly frequent recognition of coccidioidomycosis and histoplasmosis. Both of these diseases have a significantly higher incidence in males than in females. It may be presumed that the number of pregnant females with systemic fungus disease is very small and that the opportunities for, or interest in, studying their placental transmission of antibodies must be rare. One such opportunity was afforded us when we observed a young married woman with chronic cavitary pulmonary histoplasmosis for eight years, during which she bore four viable infants.[77]

Report of Cases

The present study concerns the third and fourth children born to this 31-year-old woman with histoplasmosis. The third child, a boy, was born on April 6, 1955, and the fourth child, a girl, was

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* After this paper was submitted it was learned from Dr. Charles E. Smith that he and his coworkers had reported evidence of the placental transmission of coccidioidomycosis complement-fixing antibodies in the Am. J. Hyg. 52:1 (July) 1950, and in J. A. M. A. 160:546 (Feb. 18) 1956.

TABLE 1.—*Reported Studies on the Placental Transmission in Humans of Antibodies of Various Agents Classified According to Bergey**

Order	Family	Tribe	Genus	Species	References
		Class: Schizomycetes			
I. Eubacteriales	V. Micrococcaceae		I. Micrococcus	M. staphylococcus sp.	5,12,26
	VII. Lactobacteriaceae	I. Streptococceae	I. Diplococcus	D. pneumoniae	6
			II. Streptococcus	S. sp.	7,8,10,27–32
	VIII. Corynebacteriaceae		I. Corynebacterium	C. diphtheriae	14,20,33–45
	X. Enterobacteriaceae	I. Escherichieae	I. Escherichia	E. coli	46
		V. Salmonelleae	I. Salmonella	S. typhosa	47–52
	XI. Parvobacteriaceae	IV. Hemophileae	I. Hemophilus	H. pertussis	19,21,53–55
	XIII. Bacillaceae		II. Clostridium	Cl. tetani	33,56,57
II. Actinomycetales	I. Mycobacteriaceae		I. Mycobacterium	M. tuberculosis	2,58–61
V. Spirochaetales	II. Treponemataceae		II. Treponema	T. pallidum	3,4,9,62–64
Supplement I.: Rickettsiales	I. Rickettsiaceae		II. Coxiella	C. burnetti	65
	II. Chlamydozoneceae		II. Miyagawanella	M. lymphogranulomatis	13,66
Supplement II.: Virales	II. Borreliotaceae		I. Borreliota	B. variolae hominis	67-72
				B. variolae bovis	18,73
Suborder III.: Zoophagineae			II. Briareus	B. varicellae	74
				B. morbillorum	75
	III. Erronaceae		I. Erro	E. japonicus	17
			II. Legio	L. debilitans	76
	IV. Charonaceae		II. Tarpeia	T. alpha	11,65
	VI. Rabulaceae		I. Rabula	R. infians	16
		Class: Sporozoa			
Subclass: Acnidosporidia III. Toxosporidia	Toxoplasmidae		Toxoplasma	T. gondii	15

*Bergey's Manual of Determinative Bacteriology, Ed. 6, Baltimore, Williams & Wilkins Company, 1948.

born on March 24, 1956. The former was a full-term infant of normal birth weight. The latter weighed only 2400 gm. at birth and was considered premature.

At both deliveries samples of maternal and cord blood were obtained for histoplasmosis complement-fixation tests. Whole yeast-phase antigen was used in these tests.[78] The placenta was delivered aseptically, examined in the gross and histologically, and cultured for Histoplasma capsulatum.

The third child was skin tested with histoplasmin (Lilly CT 189, diluted 1:1000, 0.1 ml. intradermally) on May 2, 1955, and again on June 15, 1955, when he was approximately 4 and 10 weeks old, respectively. The tests were read in 48 hours. Because he had a feeding problem during the first months of life, his parents were reluctant to permit further studies until he was about 4 months old. On Aug. 16, 1955, blood was drawn for a histoplasmosis complement-fixation test.

The fourth child had a more regular course of observation. Blood samples were obtained for complement-fixation tests, and histoplasmin skin tests (using Lilly antigen CTS-5, 1:1000) were repeated at approximately monthly intervals until the infant was 4 months old.

The mother's blood was tested for histoplasmosis complement-fixing antibodies at about the same time as her last child, with the exception of May 29, 1956, when no test was done. Breast milk was obtained on April 27, 1956, and on May 29, 1956, and tested for complement-fixing antibodies. The milk was also cultured for H. capsulatum.

Results

At the time of both deliveries the maternal blood showed a histoplasmosis complement-fixation titer of 1:80. The cord blood of the third child had a similar level at birth. When repeated at 4 months of age the complement-fixation test was negative. The two histoplasmin skin tests were also negative.

The cord blood of the fourth child had a titer of 1:40 at birth compared with the mother's titer of 1:80. Successively each month thereafter, the infant's titers were 1:40, 1:5, 1:5, and negative at 4 months of age (Table 2). All skin tests were negative. When the infant was one month old the mother's titer had fallen to 1:20, but it rose to 1:80 at three months postpartum and fell again to 1:40 at four months.

Both placentas were normal grossly and histologically and were negative on culture for H. capsulatum. The two milk samples were also sterile mycologically, and efforts to test for complement-fixing antibodies were frustrated by anticomplementary reactions up to a dilution of 1:20 and negative reactions in the higher dilutions.

Comment

The presence of circulating antibodies in cord blood at birth may mean either that the

TABLE 2.—*Comparison of Histoplasmosis Complement-Fixing Antibody Titers of Maternal and Cord Blood at Birth, and of Subsequent Titers of Infants Up to Four Months of Age*

Date	Age of Infant, Mo.	Histoplasmosis Complement-Fixing Antibody Titer	
		Infant	Mother
3rd child			
4/ 6/55	Birth	1:80	1:80
8/16/55	4+	0	
4th child			
3/24/56	Birth	1:40	1:80
4/27/56	1	1:40	1:20
5/29/56	2	1:5	
7/ 2/56	3+	1:5	1:80
7/25/56			1:40
8/ 8/56	4+	0	

infant has congenital disease or that a passive transfer of antibodies from mother to newborn has occurred. In most instances differentiation between active and passive immune bodies in blood serum must rest on the presence or absence of clinical evidence of disease or must await serial blood studies to show whether antibody titers decline or persist.[9] In histoplasmosis and other diseases manifested by allergy to specific antigens, it is possible to determine immediately whether a newborn child has congenital disease, provided of course that the disease is not so overwhelming that a state of anergy results. Ordinarily, the presence of circulating antibodies in the absence of skin sensitivity is indicative of the passive placental transfer of the antibodies. In time, proof of this becomes available as serum titers decline and disappear altogether within a few months after birth. Such was the case in both infants presented.

The cord blood of the third child, who was full-term, had a titer of 1:80, similar to the mother's at delivery. The last child was premature and had a cord blood titer of 1:40 compared with the mother's titer of 1:80. It has been shown that a significant direct correlation exists between the birth weight and the placental permeability[4,45] and that passive immunity is lost at about the same rate by premature and normal infants.[45] The observations presented here are in accord with these reports.

The relatively rapid loss of passively acquired antibodies has been recorded and documented by practically every investigator of placental transmission. The persistence of antibodies has varied from a few weeks to a few months. Observers generally agree that in most instances measurable quantities of humoral antibodies disappear from the infant's circulation by the fourth month of life. In this respect also, the antibodies in these two infants followed the same course of short persistence observed for the antibodies to other microbiological agents.

At this writing there is no known evidence to indicate whether the histoplasmosis complement-fixing antibodies are truly immune bodies or whether they merely represent a serological response to some antigenic but not immunity-producing fraction of the yeast phase of the organism H. capsulatum. This question is of more than academic importance. Although histoplasmosis is apparently not contagious, nevertheless the infant of a mother with the disease is born into an environment in which the probable risk of early infection may be great. Histoplasmosis in infancy is a notoriously serious disease, with a case fatality rate of almost 100%. Passive protection during the neonatal and early infancy periods resulting from the transplacental acquisition of antibodies may mean the difference between life and death for an infant who is exposed to infection with H. capsulatum at an early age, when natural resistance to infection is ordinarily low. Furthermore, if it should be proved that histoplasmosis complement-fixing antibodies are true immune bodies, serotherapy of the disease becomes a possibility.

Summary

The literature concerning the placental transmission in humans of the antibodies of 21 microorganisms is listed according to Bergey's classification of the agents.

The first known evidence of the placental transmission of histoplasmosis complement-fixing antibodies in two infants born of a mother with proved histoplasmosis is presented.

The implications of the placental transmission of these antibodies are discussed.

Drs. B. H. Woodard, of Spring Hill, Tenn., and Adolphus Bray, of Franklin, Tenn., obtained the placenta and specimens of maternal and cord blood at the time of delivery.

Dr. Charles C. Randall, Professor of Microbiology, Vanderbilt University School of Medicine, performed pathological and mycological studies of the placentas.

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Case Reports

Aganglionic Megacolon, Pheochromocytoma, Megaloureter, and Neurofibroma

Co-Occurrence of Several Neural Abnormalities

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This is a report of a patient with multiple neural abnormalities. It is presented because (*a*) multiple anomalies of a single system are traditionally of interest, (*b*) because aspects of the combination in this instance may reflect the underlying embryological error which gives rise to aganglionic megacolon,[1] and (*c*) because unrecognized pheochromocytoma is frequently associated with operative catastrophe when surgery is undertaken for a nonadrenal lesion.

Report of a Case

History.—Constipated since birth, an 18-year-old youth * had been medically discharged from the U. S. Navy in early 1955 and advised to seek surgery. Even in the neonatal period rectal suppositories had been necessary for each infrequent bowel movement. A colon roentgenogram at the age of 2 years was followed by a diagnosis of megacolon. Periodic dosing with laxatives and frequent enemas had always been necessary; nevertheless, the patient had matured normally in every way. Very occasionally, 7 or even 15 days would pass without his defecating. In adhering to the rigid routine of the military service, however, his unique practices were necessarily abandoned. Soon his rectum was impacted and hospitalization became mandatory. After suitable cleansing, the diagnosis was roentgenographically confirmed. A medical discharge was issued, and shortly thereafter the patient sought admission to the V. A. Research Hospital, Chicago.

A rather thorough review of symptoms was entirely negative, and its particulars were confirmed upon retrospective discussion with the patient's mother following necropsy. He had never experienced any type of "spells."

The blood pressure on admission was 120/80 mm. Hg, and through the period of preoperative hospitalization it did not vary significantly. Five and three-quarters feet in height, the patient was well proportioned, weighing 160 lb. Physical examination disclosed no abnormality.

Fig. 1.—Preoperative barium enema showing the dilated descending colon proximal to the normal rectosigmoid.

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* Case referred to in Medical Grand Rounds: Hirschsprung's Disease, edited by E. Clinton Texter Jr., Am. J. Digest. Dis. 1:35-46, 1956.

Laboratory.—Routine urinalysis, hemoglobin, leukocyte and differential counts were within normal limits. Electrocardiogram and chest roentgenogram were likewise not remarkable. Proctoscopy and roentgenograms in conjunction with barium enema established as narrowed the terminal 12 cm. of rectosigmoid. Proximal to this there was a massively dilated left colon (Fig. 1). The dilatation tapered toward the splenic flexure. Pyelograms, both intravenous and retrograde, established the presence of an asymptomatic right hydronephrosis and right megaloureter (Fig. 2). A level of urea in the blood serum persistently below 14 mg. per 100 ml. and an excretion of 47% of injected phenolsulfonphthalein within 30 minutes were evidences of good renal function. Smear and culture of the urine failed to demonstrate any bacteria.

Surgery.—A low anterior bowel resection, that is, the State operation,[3] was undertaken on Aug. 2, 1955. Thirty-eight centimeters of dilated (ganglionated) descending colon and narrowed (aganglionic) rectosigmoid were excised. And end-to-end anastomosis was accomplished and the peritoneum attached above the suture line.

Abdominal exploration performed upon first entering the peritoneal cavity disclosed no significant abnormality. The exploratory palpation, however, was initially accompanied by the curious development of a cardiac arrythmia and a transient hypotension such that the blood pressure was momentarily unobtainable. Exploration had to be discontinued but after a few minutes was resumed without further recurrence of the untoward rhythm or hypotension. A mild tachycardia of 120 beats per minute did, however, persist throughout surgery. Postoperatively the pulse rate and temperature rose progressively. The cause was not apparent. A Miller-Abbott nasointestinal tube and a rectal tube threaded through the anastomosis at surgery assisted in maintaining intestinal decompression. Peristalsis was evident by the third day. Bacterologic studies of the urine and blood, electrocardiograms, roentgenograms of the chest and abdomen, in addition to clinical examination, failed to elicit the cause of the tachycardia, which had risen to 160 per minute by the third postoperative day. Temperature, then, was a measured 104 F orally. Antibiotics were empirically changed from penicillin and streptomycin to tetracycline. Urine volume and electrolytes of the serum remained within normal limits during this period. There were no micrococci in the liquid feces.

Fig. 2.—Oblique view of retrograde pyelogram showing dilatation of right ureter and calyces. Preoperative film.

Peristalsis ceased by the fifth postoperative day. Shock, then coma, shortly supervened. Despite arterenol (Noradrenalin), hydrocortisone, erythromycin, and tetracycline, all given intravenously, the patient's deterioration progressed. The possibility of peritonitis prompted a desperate reopening of the abdomen under local anesthesia. All was found to be in order. A decompressing loop colostomy was established. The patient died on the sixth day after the colonic resection.

Pathology.—Surgical Specimen: The 38 cm. segment of large bowel included a 29.5 cm. dilated portion with a hypertrophied wall. The remaining proximal 8.5 cm. portion of bowel was normal in appearance and was not dilated.

Microscopically, all sections through the entire thickness of the colon showed nerve fibers in the usual positions between the layers of the muscularis and in the submucosa. Auerbach's ganglion cells were present in sections through the transition zone between the dilated and the normal bowel, as well as in the normal proximal bowel wall, but none could be demonstrated in sections taken from the dilated distal portion of the specimen (Fig. 3).

Pathology.—Autopsy: External examination revealed a recent left paramedian incision 20 cm. in length. A right paramedian incision 13 cm. long with a colostomy was present. There was subcutaneous emphysema of the abdominal wall. When the peritoneal cavity was opened, no free fluid or adhesions were noted. The site

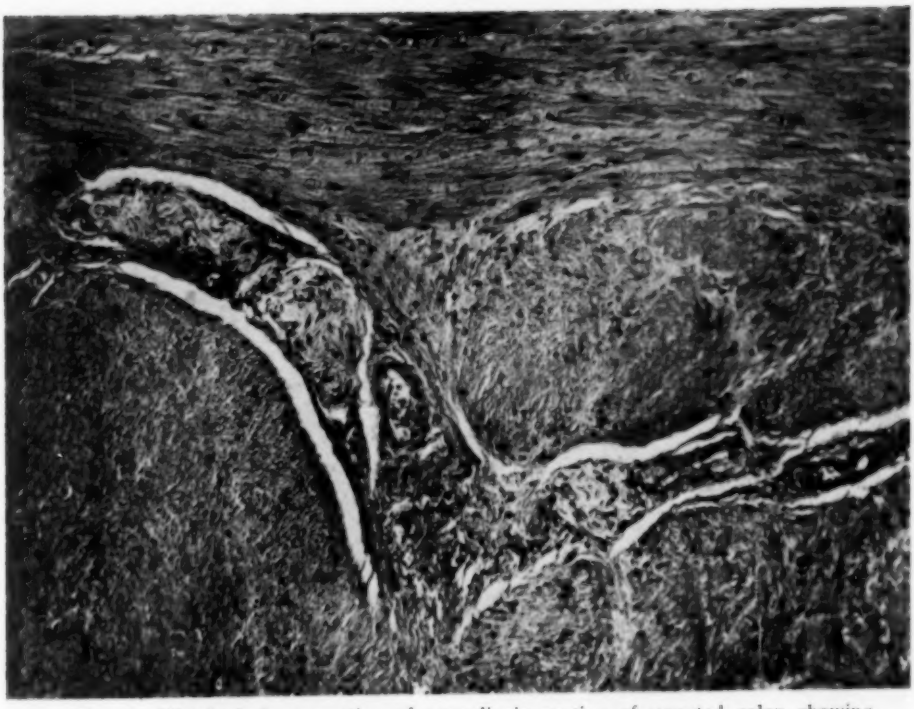
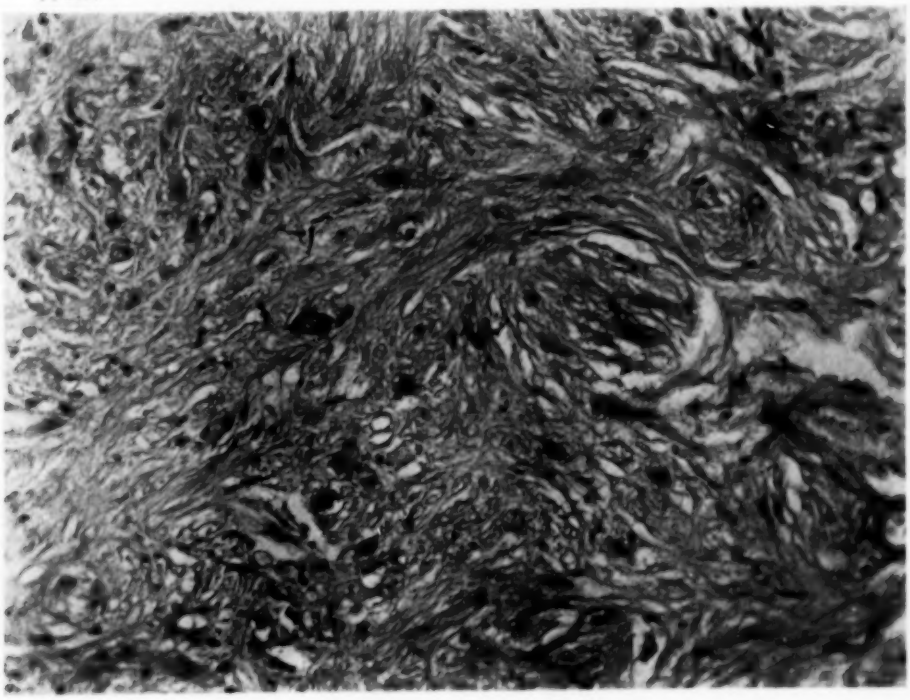


Fig. 3.—Histological preparation of aganglionic portion of resected colon showing nerve fibers but no demonstrable ganglion cells. Hematoxylin and eosin stain; mag. × 200.

Fig. 4.—Neurofibroma at aortic bifurcation. Hematoxylin and eosin stain; mag. × 400.



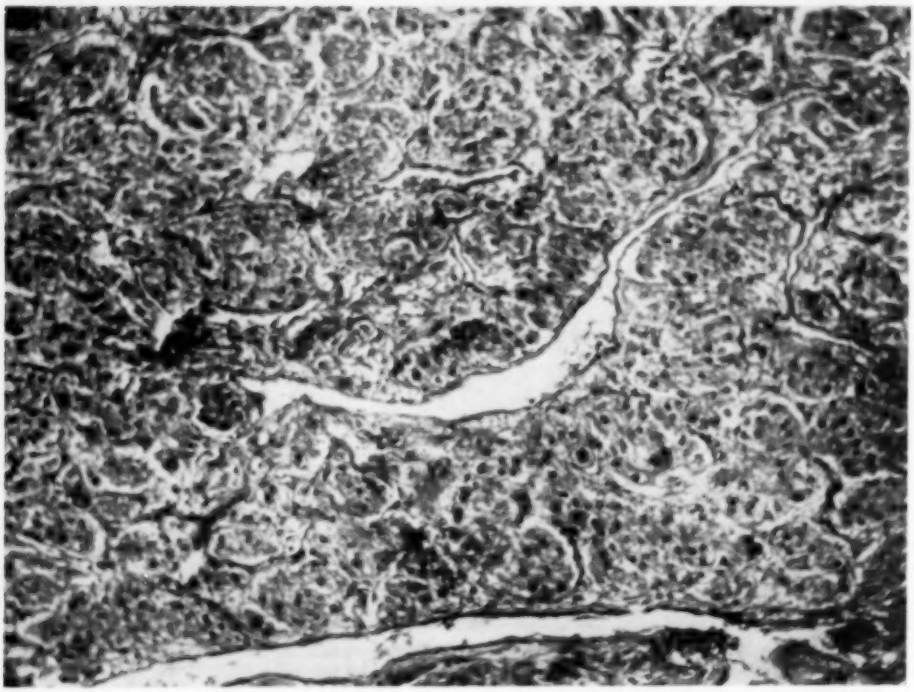


Fig. 5.—Pheochromocytoma of right adrenal medulla. Hematoxylin and eosin stain; mag. × 200.

of the recent anastomosis in the colon was intact. A round, firm mass weighing 13 gm. was found at the bifurcation of the aorta which was microscopically proved to be a neurofibroma (Fig. 4).

There was also another interesting finding at autopsy. The calyces, pelvis, and ureter on the right were all dilated. The right kidney weighed 150 gm., and the cortical thickness was only a little less than average. No obstructive lesion was demonstrated, and the ureter was followed to its entrance into the urinary bladder. The left kidney and ureter were not remarkable.

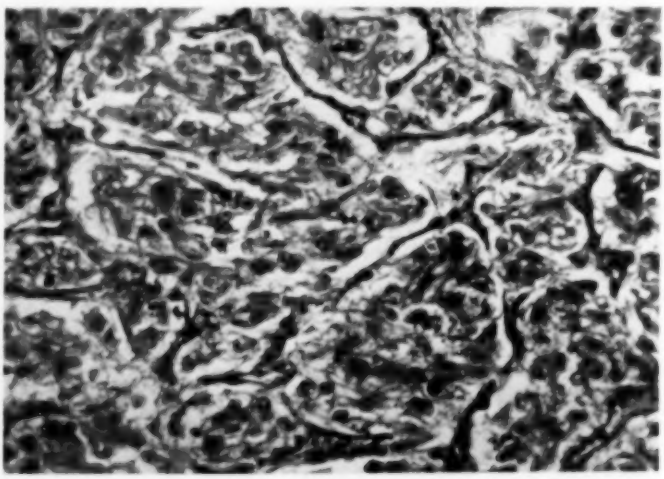


Fig. 6.—Pheochromocytoma under higher power showing characteristic arrangement of tumor cells. Hematoxylin and eosin stain; mag. × 440.

The right adrenal weighed 24 gm. Cut section revealed an encapsulated mass 2×2.5×3 cm. which had a yellowish-tan, moderately firm surface. Yellow adrenal cortex could be seen at the periphery of the mass. The left adrenal was of usual size and appearance, weighing 7 gm.

Microscopic sections of the adrenal tumor showed alveolar nests of large polygonal cells having relatively small round, slightly pleomorphic nuclei diagnostic of pheochromocytomas (Figs. 5 and 6). There was a delicate network of connective tissue between the cells. In many places the cellular arrangement resembled that of the adrenal cortex. A small portion of normal adrenal could be seen at the edge of the tumor. A thin fibrous tissue capsule was present. In an occasional area brown granular pigment was present in the polygonal cells of Zenker-fixed tissue.

Comment

The absence of myenteric ganglia (Auerbach's plexuses) in the distal colon is generally accepted as the critical deficiency in congenital megacolon. Whitehouse and Kernohan[3] in 1948 presented the cogent histologic evidence, but it was Swenson's[4] success in correcting the costive symptoms by resecting the aganglionic segment that provided the crucial physiological confirmation. Swenson et al.[5] and Hiatt[6] have studied colonic motility prior to surgery by passing multiple balloons retrograde into the aganglionic segment and beyond. By this means they have repeatedly demonstrated the absence of sequential coordinated peristaltic contractions in the aganglionic segment. Rhythmic mass motions are present but are insufficient to propel colonic contents. The proximal dilatation and hypertrophy seem to be a simple compensatory attempt to drive the contents more forcefully through the resistant aganglionic segment.

The correlation of pathogenesis with morphology is not established for megaloureter. Ganglion cells are usually found in the bladder, although their number seems to be somewhat less than normal. There is a possibility that this decrement may be more apparent than real, that is, that sections through the concomitantly dilated bladder may merely seem, on microscopic examination, to have few ganglion cells. If not stretched thin they might well appear to have the normal complement of ganglion cells. Only about 20% of patients with megaloureter have concomitant aganglionic megacolon.[7]

Embryological Aspects.—Our understanding of the embryological derivation of various neural structures evolves from ablation experiments performed primarily on chick embryos. Such data indicate that, in the chick at least, the intrinsic visceral ganglia (of both the colon and the bladder), and of the adrenal medulla itself, have a common origin. Hammond and Yntema[8] came to this conclusion after studying chicks whose thoracic and lumbar neural crests had been excised with meticulous preservation of the underlying neural tubes. Such preparations subsequently were found to be lacking peripheral sympathetic neurons, preaortic chromaffin bodies, and adrenal chromaffin cells. Removal of just the thoracic neural tube[9] of embryos yielded chicks with small but definitive adrenals.

If ablation were limited to the more proximal vagal neural crest, then subsequent chicks were found to be devoid of intrinsic visceral ganglia in the intestine, stomach, esophagus, heart, and lungs.[10] If the vagal neural crest were but incompletely excised in the embryo, then intrinsic ganglia were found in the proximal viscera but not in the distal viscera. There was no "skip area" of intestine without visceral ganglia to correspond to the short segment of ablated vagal neural crest. Rather, at some point no visceral ganglia at all were to be found caudalward although a complete complement of ganglia were present cephaled. If human embryology is not too different from that of the chick, the implications of this are most interesting, since the distal large bowel is the most caudad viscus. Thus if the distal vagal neural crest were deleteriously effected in embryo, it would be reasonable for the child to be born with no ganglia in the distal colon but with the visceral ganglia

present proximally. This, of course, is exactly the anatomical situation in Hirschsprung's disease. Likewise, a bit more extensive injury to the vagal neural crest in the embryo might well account for the occasional child born with no colonic ganglia at all, as well as for the spectrum of less extensive colonic aganglionism. With even more extensive injury to the vagal neural crest one might anticipate infants being born with visceral aganglionism extending into the small intestine. Sufficient vagal-crest impairment might so jeopardize the organism's economy as to result in its being blighted.

Alternatively, the failure of ganglia to take root in the distal colon may derive from migration failure.[1] Instead of implanting in the colon, the primitive nerve cells may have "rested" in the mesentery, along the aorta, or in the adrenal. Such totipotential cell "rests" are often hypothesized as the prime defect in neoplasia. Thus there is the possible implication of adrenal pheochromocytoma and preaortic neurofibroma in this patient. The neurofibroma was searched histologically for ganglion cells, and none were found. It should be noted that 5% of all reported pheochromocytomas have been associated with multiple neurofibromatosis.[11]

Significance of Unrecognized Pheochromocytoma.—As indicated in the protocol the patient never manifested hypertension nor had he ever experienced any sort of "spells." Whether this tumor functioned and produced arterenol is uncertain. Absence of hypertension militates against this being a functioning pheochromocytoma. The prolonged hypotension despite intravenous arterenol and cortisone is not necessarily incompatible with persistent hyperadrenalism. Persistent intravenous epinephrine (Adrenalin) can produce hypotension, shock, and occasionally death.[12,13] It is thought that the prolonged vasoconstriction and consequent reduced blood volume flow effect irreversible changes.

Some aspects of our patient's course, nevertheless, suggest that the tumor was indeed secretory. First, on initial palpation of the abdomen, possibly by compressing the tumor, the heart rate became erratic. The blood pressure, however, did not rise but, rather, fell. Perhaps this was due to the irregularity of the pulse. Second, death after fever and shock has often been reported after surgery and after parturition in patients with undetected pheochromocytoma.[14] In none of these instances in the literature, however, did the patient survive more than 48 hours postoperatively. The presented patient survived six days.

Regardless of whether this particular pheochromocytoma was active or not, the fact is that a pheochromocytoma has been found co-occurring in a patient with aganglion megacolon. Tamura and Lawrence[15] have recently reaffirmed the tendency of tumors of neural-crest derivation to occur in bewildering combinations. Aganglionic megacolon is, of course, not a tumor, but it, too, would appear to be the result of neural-crest dysfunction. Pheochromocytoma may well occur again in association with megacolon or megaloureter. If it is unrecognized in conjunction with a surgically correctable disease, the result may be catastrophic. For this reason we bring our experience to the attention of others.

Summary

The co-occurrence in a single patient of several disorders of the embryonic neural crest, namely, aganglionic megacolon, unilateral megaloureter, pheochromocytoma, and para-aortic neurofibroma, is presented. If these are of common derivation, further instances of similar co-occurrences are to be anticipated. Should the pheochromocytoma be active and unapparent, the risk of surgery, of course, is very great.

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Mediastinal Gastric Cyst

Report of an Unusual Case

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Staehelin-Burckhardt,[1] in 1909, first described the unusual finding of a gastric-lined cyst in the mediastinum. Since that time, many similar cases have been recorded in the literature. In only one instance, however, has this medical oddity been reported to involve the thoracic vertebrae. Mixter and Clifford[2] described such a patient in 1929. The following case, the second to be reported, is presented to emphasize this unusual area of involvement. It also represents a curable condition which should be considered in the differential diagnosis of lytic lesions in the thoracic spine.

Report of Case

A 42-month-old white boy was admitted to a military hospital with the chief complaint of severe episodic pain in the right hemithorax. It was located in the anterolateral chest at approximately the nipple level and had been intermittently present during the preceding 18 months. The pain appeared to come on without relationship to meals, exercise, or position. Initially it was well localized and somewhat radicular in nature. During the three weeks prior to admission, however, it was occasionally accompanied by a dull aching sensation in the back. The pain usually responded to mild analgesics but, because of the child's increased excitability, reserpine (Serpasil) also was used, with noticeable effect. Each episode of pain would last 7 to 10 days and would be followed by symptom-free periods of as long as 8 weeks. Usually, during one of the acute attacks, the pain would be most marked in the morning and again in the evening. At these times the child would remain completely immobile. No fever or other symptoms had ever been noted.

Numerous roentgenograms of the chest were taken but were always reported as within normal limits. Finally, because of the distribution of the pain, a spinal lesion was suspected and spot films of the dorsal vertebrae were obtained. These revealed suspicious radiolucent areas in the bodies of several upper thoracic vertebrae. It was this finding that precipitated the initial hospitalization. The laboratory studies, including complete blood cell count and differential count, serologic tests, blood chemistry studies, and roentgenograms of the rest of the skeleton, were all considered normal. In addition, the skin test for tuberculosis was negative. Bone marrow aspiration was not revealing, and the urine did not contain Bence Jones protein. Further roentgenograms of the spine demonstrated irregular cystic lesions in the bodies of the third and fourth thoracic vertebrae. Since the initial chest film was felt to suggest a right aortic arch, a barium swallow was performed, and this impression was excluded. Throughout this period of study, the patient continued to complain of right-sided back and chest pain. Because of the inability to arrive at an exact diagnosis without biopsy of the lesions, the patient was transferred to the pediatric service of Walter Reed Army Hospital on July 14, 1955.

The physical examination on admission was entirely negative, and additional tests were believed to be indicated. Determinations of serum inorganic phosphorus and alkaline phosphatase were, respectively, 5.3 mg. per 100 cc. and 12.2 Bodansky units. The posteroanterior roentgenograms of the chest at this institution revealed an enlargement of the superior mediastinal shadow to the right. This extended from above the level of the sternal notch to the third rib anteriorly and projected 3 cm. from the midline. In the lateral view, the mass was located posteriorly and slightly displaced the trachea before it. X-ray films of the spine confirmed the presence of a large solitary cystic lesion in the third thoracic vertebral body, with three smaller lesions in the fourth. These areas were sharply outlined by a thin sclerotic margin, and the associated interspace was slightly narrowed (Fig. 1). The radiographic picture suggested the possibility of an inflammatory process, but one of the reticuloendothelioses was felt to be a more likely diagnosis.

Because of the unusual appearance of the lesions, a percutaneous needle biopsy of the body of the

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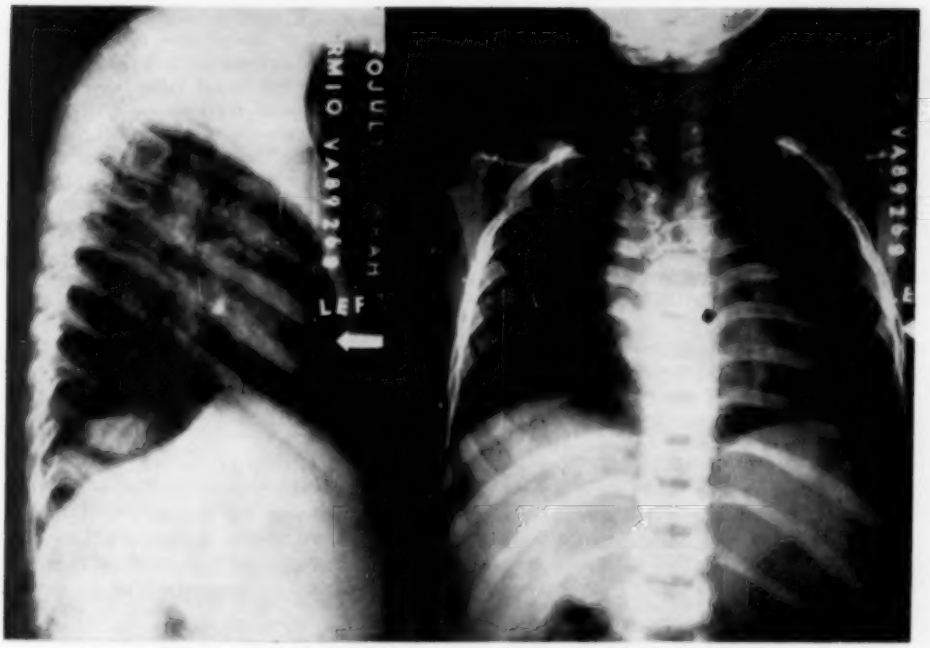


Fig. 1.—Roentgenogram of chest, demonstrating the right mediastinal enlargement and the lytic lesions in the thoracic vertebrae.

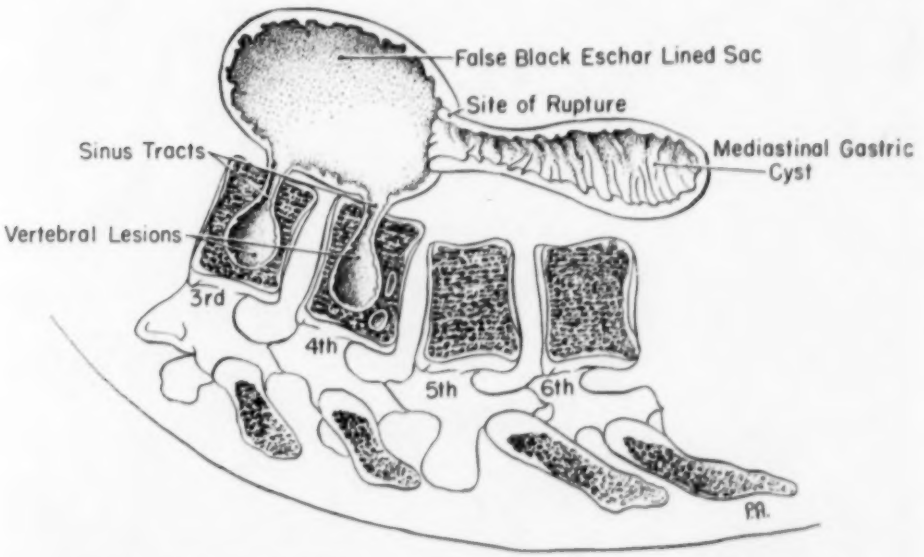


Fig. 2.—Line drawing visualizing the component parts, relationships, and communications of the gastric cyst.

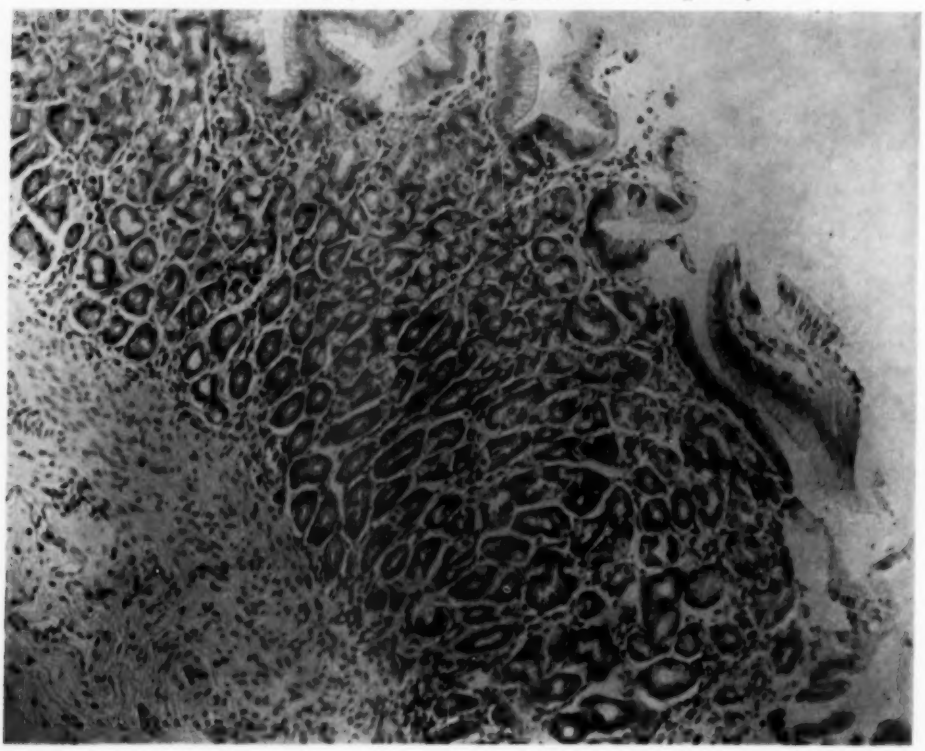
third thoracic vertebra was performed. It was observed that the bone was softer than normal but otherwise did not appear unusual. The tissue diagnosis was non-viable-appearing bone which probably represented aseptic necrosis. At this time the patient was asymptomatic and ambulatory on the ward, wearing a Taylor back brace fitted to prevent the development of a spinal deformity.

With a definitive diagnosis still lacking, more attention was then directed to the previously described mediastinal enlargement. A barium swallow was performed and demonstrated slight deviation of the esophagus to the left. For etiologic determination of the mass and also to obtain a more adequate biopsy of the diseased vertebrae, the patient was referred to the thoracic surgery service.

On Aug. 17, 1955, with use of general anesthesia, a right thoracotomy was performed. An elongated cystic-feeling mass, measuring approximately 2 cm. in diameter and 5 cm. in length, was noted paravertebrally in the superior mediastinum (Fig. 2). The surrounding tissue was both edematous and fibrotic. Needle aspiration of the unusual swelling produced approximately 25 cc. of a thin grayish fluid similar to that frequently observed in the stomach. Cultures were taken, and some of the fluid was studied for the presence of hydrochloric acid. The lesion was opened longitudinally, and the inner surface was found to be covered with a black eschar. In the depth of the cavity, sinus tracts led directly into the lytic lesions of the third and fourth thoracic vertebrae. There was also a rosebud-like area of mucosa at the lower end of the cavity. A probe could be passed through this into a blind pouch which extended distally for approximately 2 cm. The pouch was opened over the probe and appeared to be lined with gastric-like mucosa. This cystic component and the eschar-lined sac above it were completely excised, allowing the lytic lesions of the vertebrae to open directly into the right hemithorax. The chest was then closed, with one drainage tube, which was removed in 24 hours. The patient's postoperative course was uneventful.

Smears and cultures of the fluid aspirated at the time of operation were reported negative for all organisms, including acid-fast bacilli. Chemical analysis, however, revealed the presence of 25 units of total hydrochloric acid. Microscopic examination of the excised sac demonstrated normal gastric

Fig. 3.—Photomicrograph of the normal gastric mucosa lining the cyst.



mucosa with numerous acid-secreting parietal cells (Fig. 3). A final diagnosis of mediastinal gastric cyst was made.

Comment

In a review of cases reported up to 1947, Davis and Salkin [3] concluded that mediastinal gastric cysts occurred chiefly in the right hemithorax anywhere along the length of the mediastinum. Microscopically they may resemble gastric tissue in all respects, contain acid secretions, and be afflicted with peptic ulcers.

Patients have been reported from virtually all age groups, but the majority have been found in boys under 4 years of age. Symptoms are nonspecific and may be those of any intrathoracic pathological condition. Roentgen examination usually reveals the cyst as a smoothly outlined shadow off the posterior mediastinum, although secondary changes may obscure this picture.

Analysis of the findings in our patient would seem to indicate that the isolated gastric cyst ruptured into the mediastinum as a result of peptic erosion, pressure, or infection. Subsequent digestive action on the surrounding tissue would account for the black-eschar-lined false sac adjacent to the point of rupture. This is further substantiated by the presence of hydrochloric-acid-containing fluid in that area. Why the digestive process should then involve the underlying thoracic vertebrae instead of breaking into the right hemithorax is not known. That this did occur, nevertheless, is indicated by the demonstration of sinus tracts extending from the acid-containing sac to the lytic lesions in the vertebrae. The extensive destruction in the latter area is believed due to the erosive action of the acid secretion on the highly susceptible bone marrow. Simple excision was believed curative, for, without a site of origin of further insult, natural reparative processes would restore the functional and structural integrity of the thoracic vertebrae.

Summary

An unusual instance of a congenital mediastinal gastric cyst complicated by rupture, with secondary lytic lesions in the thoracic vertebrae, is reported. It is believed to be the second such case recorded. The findings emphasize the surgically curable nature of a condition which should be considered in the differential diagnosis of radiolucent lesions of the thoracic spine.

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Urethral Prolapse in Young Girls

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Urethral prolapse has been discussed mainly in the adult gynecologic and urologic literature, but the condition is not unknown in children. This paper includes a discussion of the condition in young girls together with a report of three additional cases.

CASE 1.—A 5-year-old Negro girl was admitted on Oct. 10, 1954, with a chief complaint of vaginal spotting of eight days' duration. Concurrently, she had an upper respiratory infection with a mild, nonproductive cough. Previous treatment consisted of penicillin administered intramuscularly and hot tub baths three times daily, following which she was asymptomatic for three or four days. Coincident with resumption of her usual activities the spotting recurred. There was no history of trauma or urinary symptoms prior to the onset of the presenting complaint.

Admission examination disclosed a well-developed well-nourished girl with a mild upper respiratory infection and an inflamed annular erythematous mass of prolapsed mucosa completely surrounding the urethral meatus. The urethral prolapse was very tender to palpation. Laboratory studies, including an intravenous pyelogram, were within normal limits, except for one noncatheterized urine specimen, which disclosed 10 to 20 RBC per high-power field.

Initial treatment consisted of hot sitz baths until most of the inflammation had subsided. On Oct. 13, 1954, with use of general anesthesia, pelvic and rectal examinations disclosed only the urethral prolapse. With a catheter in the bladder, the rim of prolapsed urethral mucosa was excised and sutures were placed in four quadrants; hemostasis was good. The catheter was removed 48 hours postoperatively, and the patient was discharged on Oct. 21, 1954, at which time the operative site was healing well and she was asymptomatic. Microscopic examination of the specimen revealed inflamed and congested urethral tissue.

The patient was followed at intervals in the clinic and remained asymptomatic. Two years after surgery she was asymptomatic and there was no evidence of urethral stricture or recurrence.

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CASE 2.—A 7-year-old Negro girl was admitted on Nov. 1, 1954, with a two-day history of blood having been noted on her undergarments and on the medial sides of her thighs. The mother had also noted a bloody-appearing mass in the child's vaginal area. No history of trauma, illness, or urinary complaints prior to the onset of the bleeding was obtained. The past history and family history were noncontributory.

Examination on admission disclosed a well-developed well-nourished girl with a urethral meatus entirely surrounded by an acutely inflamed, erythematous mass of urethral tissue which was tender to gentle palpation and bled very readily. Laboratory studies, including intravenous pyelography and phenolsulfonphthalein test, were within normal limits except for the presence of many white blood cells and bacteria (on culture, Staphylococcus aureus, nonhemolytic Streptococcus, Escherichia coli) in one catheterized urine specimen.

Initial treatment consisted of hot sitz baths four times daily and sulfisoxazole, 2 gm. daily, until the acute inflammation had subsided. On Nov. 9, 1954, with use of general anesthesia, a catheter was inserted into the bladder and a nonabsorbable surgical (silk) ligature was tied snugly around the prolapsed urethral mucosa. It was expected that the suture would act as a constricting band and cause pressure necrosis of the prolapsed urethral mucosa. On Nov. 12, 1954, the catheter inadvertently came out and the ligature slipped. However, on Nov. 20, 1954, the patient was asymptomatic, without evidence of the urethral prolapse, and she was discharged from the hospital.

On Dec. 7, 1954, she complained of some burning at the start of urination. On Dec. 28, 1954, she was asymptomatic, but a 16 F. urethral sound was admitted with moderate difficulty. Her urethra was then dilated with a 20 F. sound. Two years after surgery she was asymptomatic and there was no evidence of urethral stricture or recurrence.

CASE 3.—A 2½-year-old Negro girl was admitted for the second time on Dec. 19, 1954, with a complaint of vaginal bleeding. She had been in good health until four hours prior to admission, when bleeding from the vaginal area was observed when the patient urinated. There was no history of urinary symptoms, except enuresis, or trauma to the genital area prior to the onset of the bleed-

ing. Her previous admission had been at age 5 months, for a subdural hematoma following cephalic trauma. Her past history, otherwise, and the family history were noncontributory.

Examination on admission revealed a well-developed well-nourished girl with tinea capitis secondarily infected and an acutely inflamed, tender, hemorrhagic, edematous mass of prolapsed mucosa entirely surrounding her urethral meatus. Laboratory studies were all within normal limits (Fig.).

On Dec. 27, 1954, cystoscopy revealed no abnormalities except the urethral prolapse. With a catheter in the bladder, a simple excision of the prolapsed mucosa was performed. The denuded area was approximated with four chromic absorbable surgical (gut) sutures, and the catheter was left in the bladder for 48 hours postoperatively. The patient was discharged from the hospital on Jan. 3, 1955, asymptomatic, with healing of the operative site. No follow-up visit has been available.

Comment

The frequency of urethral prolapse in females has yet to be established. Some authors [1-4] consider it rare, but Begg [5] has suggested that urethral caruncles are really partial urethral prolapses and, hence, a fairly common condition. There is some agreement that the occurrence of urethral prolapse is higher in childhood and old age,[2,4,6-9] with the years 8 to 12 as apparently the peak ones,[4,9] although Campbell [10] cites early infancy as another period of high occurrence. Since 1944 there have been at least 20 cases of urethral prolapse in girls reported.[2-4,9,11-17] A racial predilection for Negro females has been suggested.[11]

Many possible causative factors have been suggested regarding the etiology of urethral prolapse. Zeigerman [9] reports two cases in young girls; in one, constipation and a persistent cough and, in the other, trauma to the vulva are mentioned as probable causative factors. Foix's [2] case, occurring in a child who previously had a rectal prolapse, would tend to support the etiologic theory of congenital weakness of the pelvic structures. Abrams and Lewis [11] presented five cases in Negro girls between the ages of 3 and 8 years. Trauma was considered causative in two cases; severe coughing, in the third; the other two were of undetermined etiology. Most of the cases reported have been of undetermined etiology.[3,6,12-17] No definite causative factor could be demonstrated in the cases reported here.

Campbell [10] describes the lesion as a reddish or reddish-blue meatal tumor, very sensitive and bleeding easily. Zeigerman [9] suggests that the muscular layer is absent in prolapse of the urethra, but whether or not there is a change in the elastic tissue has not been demonstrated conclusively. Inflammation and edema of the prolapsed mucosa are common; degenerative changes, such as ulceration, necrosis, or gangrene may occur in the more advanced lesions. The cases herein reported all showed a concentric, annular herniation of the mucosa through the meatus, consistent with a complete urethral prolapse, and were inflamed, edematous, extremely tender, and bled on slightest palpation but were not gangrenous.

The commonest presenting symptom in young girls is bleeding or spotting from the vulvovaginal region. Urinary complaints of varying severity also may be present. Typically, the bleeding is noted on the child's undergarments or at urination. Occasionally, the presence of a mass in the vagina may be one of the main complaints.[4,11,15]

The onset of the symptoms often is acute. From the literature, there is no consistent correlation between the type of symptoma-

tology and the duration of the lesion. It might be conjectured that in those children in whom sudden vaginal bleeding was the first symptom the condition should be of shortest duration. This is not borne out by the reports, in which some children were noted to have had intermittent vaginal bleeding for many months or frank bleeding for long periods before treatment.[2,4,11,15,17]

The diagnosis of urethral prolapse is made almost exclusively on the characteristic clinical appearance of the lesion. The differential diagnosis includes urethral caruncle, polyp, prolapsed urethrocele, condylomata, prolapsed bladder, and carcinoma of the urethra, the last being rare in young girls.[15]

Various methods have been described for treatment of the lesion. Conservative treatment, consisting of hot sitz baths followed by attempted digital replacement of the prolapsed mucosa, provided it is not gangrenous, has been mentioned as initial therapy but has not been cited as successful definitive treatment. Moffett and Banks[15] and Barns[12] routinely employ the above as a preparation for surgery. The simplest surgical procedure consists of insertion of a catheter into the bladder and placement of a suture encircling the prolapsed mucosa, resulting in necrosis and slough of the prolapsed mucosa. Doria[14] considers this the method of choice. Moir,[16] Barns,[12] Zeigerman,[4,9] and Pereira[3] claim excellent results with circumferential excision of the prolapsed mucosa and suturing of the cut mucosa—either continuous, interrupted, or in quadrants. Foix,[2] Abrams and Lewis,[11] and Moffett and Banks[15] report success with complete circular excision of the prolapsed mucosa with the cautery, without the use of sutures, as the cautery is believed to be sufficient for hemostasis. Penaud[17] combines the two methods—excision by the cautery and suturing the mucosa—and claims good results. The necessity for an indwelling catheter for varying periods of time following surgery remains unsettled. Two of the patients (Cases 1 and 3) were treated by surgical excision of the urethral prolapse and suturing the mucosa, with good results. Another patient (Case 2) was treated with a ligature tied around the prolapsed mucosa over an indwelling catheter, with good results insofar as removal of the prolapse was concerned, but later some tightness of the urethra developed. Other surgical procedures—Hepburn procedure[18,19] and Watkins anterior vaginal plastic procedure[9]—have been used, but discussion of them is beyond the scope of this paper.

The chief complications incident to surgery are urethral stenosis and resultant stricture, urinary incontinence, and recurrence of the urethral prolapse. No recurrences after surgical therapy in young girls have been reported. To guard against urethral stricture, Abrams and Lewis[11] recommend weekly and then monthly urethral dilatations for two to three months following the patient's discharge from the hospital. Penaud[17] reports a 12-month follow-up with no urinary complaints or recurrence of the urethral prolapse. Moir[16] reports one case with an 18-month follow-up in which his patient had no abnormalities except some urinary urgency. Two of the patients (Cases 1 and 2) reported here show no evidence of recurrence or urinary complaints two years after surgery.

Summary and Conclusions

Three cases of urethral prolapse in Negro girls, ages 3 to 7 years, with acute onset and vaginal bleeding or spotting as the presenting complaint, are reported. Two patients were treated by excision and suturing the cut urethral mucosa; one, by ligature of the prolapsed urethral mucosa over an indwelling catheter. Results were about the same in all three cases. A brief discussion of urethral prolapse in young girls is included.

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Correspondence

MEMORANDUM ON LEGISLATION REGARDING THE ENTRY OF MIXED-BLOOD ORPHANS INTO THE UNITED STATES FOR ADOPTION

To the Editor:—The most needy children in the world today are some thousands of mixed-blood orphans left behind by Occupation forces in Korea, Japan, and Okinawa. Their numbers are unknown, and they are still being born. The onus of being the children of conquerors lies heavily upon their innocent shoulders. The onus of being half-white lies still more heavily. They are discriminated against in countries already poor and overpopulated. In cultures where it is difficult, if not impossible, to find jobs except under the sponsorship of family, they will have no families to help them as they reach adolescence.

Yet to their plight the American public has remained indifferent, although most of them are fathered by American men. As these children grow into displaced adults it is all but inevitable that they will become centers of rebellion and revolution. Their hatred will turn inevitably to those who have brought them into being and then rejected them. It cannot be wise, surely, to allow half-white children, most of them half American, to grow up in Asia as the lowest class of citizen. It cannot add to the prestige of our own people or the white man, if this takes place. Yet it is taking place, and will take place increasingly, unless something is done for these orphans while they are still children.

Paradoxically, thousands of adoptive parents in the United States want the children. Homes are ready and waiting for them. Money is no problem. The problem is that at present not one of these orphans is allowed to enter the United States. Organizations and individuals who have heretofore with heroic effort and by many devices brought in a few children can bring in no more. While cynicism about our brand of democracy mounts in those parts of the world where half-American children live unwanted and too often neglected, let us examine the situation in Washington regarding their plight. Why is there no legislation which would allow them to come to waiting adoptive homes?

Briefly, here are the facts:

When the Refugee Relief Act expired in 1956, President Eisenhower requested and Commissioner Swing authorized the parole into the United States of orphans who had been adopted or whose adoption was under consideration. This was an emergency measure, taken when Congress was not in session, and it is now ended. An extension of the parole has been denied, on the grounds that it would be inappropriate at a time when Congress has pending before it legislation introduced for the purpose of alleviating the plight of the orphans. The legislation now proposed is as follows:

The President's own immigration program, submitted to Congress on Jan. 31, 1957, contains Section 208, authorizing the issuance of 2500 non-quota immigrant visas annually to eligible orphans who have been or will be adopted by United States citizens.

The Bill, S.1006, introduced by Senator Watkins, provides for needed changes in our immigration laws and also contains a section allowing an annual quota of 2500 orphans.

Congressman Walter's Bill, H. R. 4008, provides for an orphan quota of 5000.

Senator Neuberger's and Senator Morse's Bill is S.866, and it provides for the entry of 10,000 orphans to adoptive homes in the United States. Congressman Porter has an identical bill.

Congressman Cellar's new omnibus bill in the House is H. R. 3364.

There is an encouraging amount of interest in the mixed-blood orphans in Japan and Korea and Okinawa on the part of some Congressmen, and yet months pass by and the bills thus far introduced are not passed. They are being held more or less permanently in Committee, for reasons unknown. Of all the refugees into our country, these children are the most innocent. They, at least, are incapable of being communists and therefore security risks. In Korea alone, I am informed by Joon Mo Chung, Minister of Health and Social Affairs of the Republic of Korea, in a letter to me dated Feb. 27, 1957, there are approximately 550 mixed-blood children waiting for adoption. Here on this side of the ocean, adoptive parents also wait in vain. It

may be argued that other and more pressing matters face Congress. Is there anything more pressing in the world today than orphans in their need? Children soon grow out of childhood. A few months, a year or two, and then adoption is increasingly difficult until it is impossible. The adjustment cannot be made. It is too late. Children remain homeless and parents childless. Only today I have received a letter from a United States Senator who writes as follows:

"I have been disappointed that Congress has not as yet taken some positive action on the non-controversial orphan legislation. Despite the good words of the Administration, they have continued to drag their feet. The Chairman of the Senate Immigration Subcommittee, Senator Eastland, on January 30 requested reports on my Bill from the Attorney General and the Secretary of State. The Secretary of State's report was received two weeks ago but the report from the Attorney General has not as yet been prepared.

"I feel that the vital and non-controversial orphan legislation should be kept separate from the highly controversial general changes in the immigration laws. Our problem lies not in the fact that the orphan legislation is controversial but that a large portion of the members of Congress feel that it is not of sufficient importance to be considered at this time."

The passage of a simple noncontroversial bill, allowing for the entry of a specified number of orphans for waiting adoptive homes, would take only a few minutes and no money. Parents pay all costs.

Delay then is only an excuse, for reasons unknown. It is time to inquire why the delay, and what the reasons.

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Abstracts from Current Literature

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Congenital Nonspherocytic Hemolytic Anemia: Two Nonfamilial Cases with Red Cell Survival Studies.—The authors state that in the past several years "nonspherocytic hemolytic anemia" has been separated from the previously identified groups of congenital hematological disorders. It is characterized by macrocytosis, basophilic stippling, hepatosplenomegaly, and jaundice. It usually starts in infancy and may simulate erythroblastosis fetalis. By various techniques it can be separated from thalassemia, familial spherocytosis, and hemolytic anemias based on molecular abnormalities of hemoglobin and from acquired hemolytic disease. Evidence suggests that it be considered as a clinical and pathological entity. Several workers have demonstrated, by cross transfusion studies, that there is an intrinsic defect of the red cells. Most of the previously reported cases have shown evidence of a genetic basis. The authors report on two cases that did not have a genetic basis.

The first case was a 6-year-old girl who was noted to have jaundice, hepatomegaly and a Hgb. of 12.2 gm. at 24 hours of age. The jaundice gradually disappeared, and then the child was noted to be very pale. She had several hospital admissions. Characteristic findings were hepatomegaly and pallor. Hematologically her hemoglobin was usually about 7.0 gm.; reticulocytes, about 10% to 20%; basophilic stippling was noted; there were normal fragility test, normoblastic hyperplasia of bone marrow, negative Coombs' test, both direct and indirect, elevated fecal urobilinogen, elevated erythrocytic protoporphyrin, normal hemoglobin electrophoretic pattern, normal liver-function tests, negative urine test for lead, and no siderocytes or hemosiderin deposits in bone marrow. With use of radioactive Cr^{51}, the patient's red cells were tagged and showed a marked reduction in red cell survival time in a normal person, whereas normal, tagged, red cells showed only a slightly shortened survival time in the patient. Radioactive Fe^{59} was cleared from the patient's plasma much more quickly than normal.

The second patient was a 3-year-old boy who had been found to have severe anemia and hepatosplenomegaly at the age of 3 months. Hgb. was 6 gm.; fragility, normal; Coombs' test, negative; 18% normoblasts; bone marrow showed erythroid hyperplasia (all at age 9 months). A splenectomy was performed at this time. This had no effect on the anemia. When the patient was seen by the authors, the laboratory studies were essentially the same as those of the previous case. Red cell survivals were of the same order as in Case 1, with the patient's cells

showing markedly shortened survival and normal cells showing just slightly shorter survival than normal when injected into the patient. Because of this and because of the frequently required transfusions and because a negative Coombs test is rarely found in immunological mechanisms, the patient was reexplored, and a large accessory spleen was found. Cortisone had been tried, with no results. The splenectomy had no effect on the hemolytic state, although there was a temporary decrease in the requirement for transfusion.

In their discussion of the disease the authors note that macrocytosis is a rather constant finding. In many cases the urinary coproporphyrins were increased, and in Case 1 there was a reversal of the isomers. They speculate that a defect in hepatic metabolism might be responsible for the macrocytosis, the disturbed prophyrin metabolism, and the formation of abnormal red cells. In several cases the serum iron has been low, there has been a lack of siderocytes, and the punctate basophilia has been shown not to be iron. These findings have the paradoxical picture of iron-deficiency anemia in the presence of a hemolytic picture. The authors theorize that possibly the reticuloendothelial system retains iron in a particularly insoluble form. This might also explain the rapid removal of tagged iron from the plasma (or it might be due to increased utilization of the hyperplastic erythroid system).

The authors also felt that their cases did have a slight extracorpuscular defect, probably from hypersplenism, since the survival of normal cells in the patients was slightly lower than normal.

Pneumatosis Cystoides Intestinalis in Children: Report of a Case Complicated with Fatal Pneumoperitoneum.—The author states that of 252 cases of pneumatosis cystoides intestinalis in the literature only 42 have been reported in children. He reports the first case from Turkey. The child was 3 months old and had had a history of three weeks of an upper respiratory infection with diarrhea which did not respond well to treatment. Coughing was fairly severe, and the day before admission abdominal distention became severe, seemingly after a severe coughing episode. Physical examination showed poor nutrition with slight dyspnea and dehydration. The abdomen was markedly distended, with obvious venous engorgement. It was extremely tympanitic, and the liver could not be percussed. A few rales were present over both lung bases. Hgb. 9.0 gm.; WBC 10,200, with 60% polymorphonuclear cells and 4% young forms. Urine, negative. Stools were watery, bright yellow, but without mucus or blood. The child was treated with antibiotics, but there was no change the next day, and x-rays then showed pneumoperitoneum. Paracentesis was done, with removal of 400 cc. of air. There was temporary improvement, but air reaccumulated in spite of more paracenteses and the child went downhill and died. Autopsy revealed marked distention of intestines, with numerous gaseous cysts disseminated in the transverse colon; there was a true megacolon of the transverse colon; in this same area were numerous superficial lenticular ulcerations of the intestinal mucosa, chiefly in the area of narrowing of the distal part of the transverse colon. Dye injected into the trachea and into the intestinal tract before the abdomen was opened did not find its way into the peritoneal cavity.

In his discussion the author states that the gaseous cysts are usually noted in the small and large intestine, particularly in the terminal ileum, ascending colon, and the jejunum. In children they are usually seen under the mucosa. The composition of the air is close to that of atmospheric air. There are two theories as to the pathogenesis: according to one, the cysts are produced by gas-forming bacteria; according to the second theory, the air penetrates the mucosa through ulcerations. The first theory is being discarded because it does not fit the facts very well. In his case the author felt that the pneumoperitoneum was due to rupture of the cysts, which were subserosal in this patient. He postulated that the severe coughing may have played a part in the rupture of the cysts. He also speculates as to the possibility that laparotomy might have been helpful, but he points out that neither the megacolon nor the cysts were diagnosed by x-ray. He concludes by pointing out that the diagnosis is very difficult.

Chronic Staphylococcal Enteritis in Infants.—The author notes that the Staphylococcus has always been a troublesome organism to both the clinician and the bacteriologist, especially since the introduction of antibiotics. It has shown an amazing ability to change its characteristics and to adapt to adverse circumstances. The question then comes up as to whether or not it may change in pathogenic qualities. The author believes that the present article gives some support to the idea that it may do so. The present article deals with a chronic disease pattern.

The syndrome described consists of diarrhea with foul-smelling stools containing mucus and sometimes blood. The infant is usually artificially fed, and the symptoms of nine infants

were present from the time of discharge from the hospital or started soon after discharge. The infants were fussy but not acutely ill and were treated as feeding problems. The nine cases reported varied in age from 13 days to 4½ months when the author first saw them. All had staphylococci in their stools. Several had recurrences, and staphylococci were found during the recurrences. Late treatment, which occurred in two cases, seemed to be much less effective in clearing up the condition.

In the discussion of this syndrome the author states that it appeared that the bacteria were contracted in the nursery. Forty-three babies, selected at random in one week, had stool cultures done, and 10 (23.3%) were positive for coagulase-positive staphylococci but had no symptoms. He states that, although this syndrome appears to be much more common than was previously suspected, there may be a carrier state and one should not neglect searching for other causes of enteritis.

The Effect of Vinegar on the Growth of Enteric Bacteria in Evaporated Milk Mixtures.—Because of an article by Seymour and associates on the bactericidal effect of acidified milk, the author carried out studies on the growth of Escherichia coli and Shigella flexneri in acidified milk mixtures. In reviewing some of the basic work in this field, the author refers to the known fact that the acetate ion and the undissociated acetic acid exert a specific toxic inhibitory effect on the growth of various bacteria, particularly the Gram-negative bacteria.

The author determined the growth curves of the selected bacteria in unmodified and the acidified evaporated milk mixtures. This was carried out over a 24-hour period. The basic evaporated milk formula was 40% evaporated milk, 3% dextrose, and 57% water (13 oz. evaporated milk, 17 oz. water, and 2 tablespoons of sugar). When modified with vinegar, the proportions were 40% evaporated milk, 3% dextrose, 4% vinegar (containing 4% to 5% acetic acid), and 53% water. All ingredients were purchased at the grocery store. The final concentration of acetic acid was 0.224%, or 0.037 M.

The addition of the vinegar showed a marked inhibitory effect on E. coli and some bactericidal effect so that at the end of 24 hours the medium was in effect sterilized. The effect of the added vinegar on Shigella flexneri was even more striking; by six hours the culture was practically sterilized. Studies were repeated on another culture of Shigella flexneri at 37 and 20 C, with the same effect on both. This species was inhibited and not killed by the acetic acid.

The author feels that the use of vinegar for the inhibition of bacterial growth has a special place for those groups of people who have poor refrigeration facilities in various parts of the world. He mentions that in this country there is a large migrant farm labor group (over 1,000,000) which have high rates for epidemic and diarrheal diseases. He feels that the use of vinegar in the milk would afford a significant improvement in the health of the infants.

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* The Treatment of Tetanus by Sedation, Curarization, and Intratracheal Positive-Pressure Artificial Respiration, With Report of a Case. P. M. Last and Judith Nicholas.—p. 373.

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2, No. 14 (Oct. 6) 1956

Hypothermia Control with an Improved Plastic Blanket. M. H. Cass.—p. 509.

2, No. 15 (Oct. 13) 1956

Notes on Argentaffin (Carcinoid) Tumours: Three Examples in Childhood. Reginald Webster and Alan Williams.—p. 553.

The Treatment of Tetanus by Sedation, Curarization and Intratracheal Positive-Pressure Artificial Respiration, with Report of a Case.—The successful treatment of a severe case of tetanus is described. The treatment consisted of sedation, curarization, and positive-pressure artificial respiration for six days. These were instituted because of extreme respiratory difficulty. The positive pressure was maintained through a tracheotomy. More routine therapy included antitoxin serum, penicillin therapy, broad-spectrum antibiotics, and debridement of a compound fracture. Of interest in this case was the fact that the fracture occurred in February, at which time the patient received 5000 units of antitetanic serum. Several surgical procedures were carried out, owing to malunion of the fracture. The last surgical procedure was carried out in late August, two years later, at which time the wound became infected. First evidence of tetanus occurred 17 days after the last surgical procedure. This was manifested by trismus. At the time of onset of these symptoms the patient received 80,000 units of tetanus antitoxin and over the next 12 days, four more doses, totaling 265,000 units. In spite of these doses the patient went on to develop severe tetanus with marked respiratory difficulty necessitating the above measures. The authors speculate that failure of the antitoxin to control the disease in this patient may be due to the formation of antibodies by the patient against the modified horse globulin of the antitoxin. "After a certain stage, possibly seven to ten days after the initiation of intensive antitoxin treatment, the antitoxin will be rapidly removed from the circulation, as a result of reaction with these antibodies. Under these circumstances the therapeutic effect may be negligible."

Medizinische Klinik, Munich

51, No. 43, 1956

Prophylaxis of Infections by Means of Nonspecific Stimulating Therapy. F. Haggemueller.—p. 1833.

51, No. 44, 1956

Treatment of Infections in Childhood with Hostacyelin. A. Banckholt.—p. 1874.

51, No. 45, 1956

15000 Epivan.—Narcoses. A. Vogl.—p. 1905.

51, No. 46, 1956

The Syndrome of the So-Called Small Attacks.—G. Struck.—p. 1955.

51, No. 47, 1956

The Problem of Psychotherapy in Children. E. Stearn.—p. 1981.

51, No. 48, 1956

* Epidemic Hepatitis in Children. V. Kredba.—p. 2033.

Epidemic Hepatitis in Children.—Over a period of six and one-half years 10,203 children with epidemic hepatitis were treated in a hospital in Prague for infectious diseases. The ages varied from 2 months to 14 years. Only 25 cases occurred in infants. Within the two-year limit of age, 2.29% occurred. The age-group of 3 and 4 years furnished 10.21%; that of 5 and 6 years, 20.63%. The 7- and 8-year-old group contributed 24.05%; the 11- and 12-year-old group, 13.46%, and the 13- and 14-year-old group, 8.34%. The largest number of cases fell in the fourth trimester of the year. The probable source of infection could be determined in 67%. Over the years the diagnosis improved, and so admissions during the first three days of the disease became much more frequent and the incidence of cases in which the diagnosis was delayed past the 14th day of the disease dropped from 12% to 2%. The importance of history, with due emphasis on epidemiological factors, and of clinical observation for early diagnosis is stressed, particularly with regard to the anicteric phase. Overevaluation of functional tests can interfere with early diagnosis, since a positive response may be wanting. On the functional tests, the determination of the aldolase activity of the blood serum is mentioned, particularly. A positive response is reported in 207 of 226 ascertained cases of epidemic hepatitis. The number of other cases of icterus or liver involvement was very insignificant. Passive immunication by means of γ-globulin proved very successful. The preicteric phase was studied, especially, in 3000 cases. In about one-third it could not be

determined. In about three-fifths of the cases it lasted one to three days. In a number of cases it extended over five days, and it could exceed six days.

It is noted that the preicteric phase was afebrile in 46%. The frequency of various symptoms is given. Pain in joints and in the muscles occurred infrequently at this time; neither were many cases of exanthema seen. While the disease is rather infrequent in infants, 8 of the 25 cases died. More severe cases are seen up to school age than later on, when the course of the disease is usually mild. There are some cases running an uneven protracted course, entailing the danger of liver dystrophy or of chronic liver damage. The influence of other infectious diseases during the incubation period is discussed, as well as the aggravating influence of the hepatitis on other diseases, for instance, upper respiratory tract infections. On the other hand, the hepatitis may minimize the lesions of chickenpox and measles. Late diagnosis, with its absence of treatment, favors a protracted course. The most important features of treatment are bed rest and diet. The diet, after the initial anorexia, nausea, and vomiting, contains milk and milk products as a source of protein. Later a certain amount of meat is added. Light and moderately severe cases need no other treatment. Other therapeutic measures are discussed for cases of greater severity, but it is questioned whether such therapy can accomplish more than bed rest and diet, depending on the severity of the disease or on relapses. Attendance at school is delayed from 6 weeks to 12 months. Excluding cases admitted as incipient liver dystrophy, the total mortality was 0.08%. Recurrence and relapse occurred in 0.78%; their course is likely to be more severe.

Monatsschrift für Kinderheilkunde, Berlin

104, Aug., 1956

Changes in the Electrocardiogram of Children Receiving Megaphen (A Phenothiazene Derivative). Heinz Kupatz.—p. 335.
Treatment of Pleural Empyema in Children. E. F. Schmidt.—p. 340.
Infantile Scurvy. Hans-Wolfgang Ocklitz.—p. 343.
* Treatment of Chorea Minor with Phenothiazine. Ilse Woelfer.—p. 352.
* The Problem of Abscess-Forming Pneumonias. Karl Nissler and Elisabeth Plassmann.—p. 356.
Chorea Minor with Peripheral Facial Palsy. Hermann Stutte & Beate Gehrt.—p. 359.
Review Article: Tuberculosis. A. Wuderwald.—p. 362.

104, Sept., 1956

Differential Diagnosis of Chronic Polyarthritis in Childhood with Special Emphasis on Wissler's Subsepsis Hypergica. Malte Kienitz.—p. 371.
* The Question of Food Aspiration in Hypertrophic Pyloric Stenosis. J. K. Dittrich.—p. 374.
Individual Variations in the Levels of Dold's Inhibins in Raw Human Breast Milk. M. Spruessig, G. Essigke, and H. Koeditz.—p. 380.
Congenital Dystrophic Angiectasia (Klippel-Trenaunay-Weber Syndrome). Robert Beckman and Fritz Koch.—p. 384.
Fibrous Dysplasia in Childhood. Rolf Mueller.—p. 387.
Carcinoma of the Thyroid and Cushing's Syndrome. Herbert J. Burgstedt.—p. 395.

Treatment of Chorea Minor with Phenothiazine.—Nine children with chorea minor were treated with phenothiazine preparations (Megaphen and Propaphenin). Dosage was 1 mg/kg. three to four times daily, administered orally. Average doses were 75 to 100 mg/24 hours.

Decrease in motor activity and psychological benefits were remarkable. They were attained within three to eight days after onset of therapy.

It was felt that treatment should be continued for three weeks, although it was not ascertained whether a shorter period might suffice. Children with relapses of chorea minor required higher doses and more prolonged treatment periods. One patient with chorea minor due to encephalitis was not benefitted by phenothiazine therapy. One patient suffered a relapse after two weeks. No toxic effects due to the drug were noted.

The Problem of Abscess-Forming Pneumonia.—The number of children at the Children's Hospital of Magdeburg, Germany with abscess-forming pneumonias rose from an average of 9 cases per year between 1948-1950 to 66 during 1955.

Between 1948-1950 a total of 17% of these patients developed the disease process during hospitalization, whereas during 1955 it occurred in 41%.

Infants during the first four months of life were affected most frequently (43%). Over-all mortality was 40%; it had been 34% between 1953-1955 and 50% in previous years.

Spontaneous pneumothorax was observed in 13% in the earlier years and in 37% between 1953-1955. Total was 75 children. In 39 of these thoracocentesis with insertion of a rubber drain was performed. Five children died when this procedure was undertaken. No satisfactory explanation for the increase of abscess-forming pneumonia could be given.

The Question of Food Aspiration in Hypertrophic Pyloric Stenosis.—Repeated roentgenological examinations were performed on 67 infants with hypertrophic pyloric stenosis in order to confirm the signs of food aspiration as reported by Seelig. These were said to consist mainly of mediastinal changes, such as mediastinal pleurisy and tracheobronchial lymphadenitis. It was found that these changes occurred only rarely and could not be specifically related to food aspiration. It seemed plausible that spastic vomiting prevented such an occurrence.

New England Journal of Medicine, Boston

255, No. 13 (Sept. 27) 1956

Thrombotic Thrombocytopenic Purpura: Report of a Case, with a Review of the Pathogenesis of the Disease. S. Soumerai and W. F. MacGillivray.—p. 585.
* Extreme Polyuria in Obstructive Uropathy: Report of a Case of "Water-Losing Nephritis" in an Infant, with a Discussion of Polyuria. L. E. Earley.—p. 600.
Diseases of Medical Progress. R. H. Moser.—p. 606.
A New, Effective Shampoo Treatment in Seborrhea Capitis. E. F. Finnerty.—p. 614.

255, No. 14 (Oct. 4) 1956

The Natural History of Infectious Disease In A Boy's School, 1900-1956. T. H. Ingalls.—p. 629.
* Host Influence on Upper Respiratory Flora. M. B. Dunlop and H. S. Harvey.—p. 640.
Medical Progress: Application of Homeostatic Principles to the Management of Nephritic Patients. N. B. Talbot, J. D. Crawford, G. A. Kerrigan, D. Hillman, M. Bertucio, and M. Terry.—p. 655.

255, No. 15 (Oct. 11) 1956

* The Analgesic Properties of Numorphan (14-Hydroxy Dihydromorphinone): A New Synthetic Narcotic. A. Coblentz and H. R. Bierman.—p. 694.

255, No. 16 (Oct. 18) 1956

* Electrophoretic Analysis of Serum Proteins in Infants and Children: I. Normal Values from Birth to Adolescence. J. W. Oberman, K. O. Gregory, F. G. Burke, S. Ross, and E. C. Rice.—p. 743.
Observations on Urticaria in Childhood. I. H. Schwartz.—p. 771.

255, No. 17 (Oct. 25) 1956

* Prevention and Control of Postoperative Wound Infections Owing to Staphylococcus Aureus. C. W. Howe.—p. 787.
Systemic Treatment of Primary Tuberculosis. R. Debré.—p. 794.
Agranulocytosis Associated with Chlorpromazine Therapy: Report of a Case and Review of the Literature. G. Schick and J. Virks.—p. 798.
Medical Progress: Proctology. E. P. Hayden.—p. 809.
Thalassemia in a Family of Pure German Extraction. J. E. Middlebrook.—p. 815.

Extreme Polyuria in Obstructive Uropathy: Report of a Case of "Water-Losing Nephritis" in an Infant, with a Discussion of Polyuria.—The author reports a case of polyuria with polydipsia in an infant with obstruction of the bladder neck. The infant, admitted at age 6 months, had a history of almost constant urinary infection since the age of 7 weeks; at 4 months he was noticed to have a marked increase in frequency of urination and in thirst. On admission he was small, irritable, and had a distended bladder which did not empty; kidneys appeared enlarged. Urine was infected with resistant organisms. Specific gravity was low. Studies revealed partial obstruction of the internal urethral orifice by hypertrophied tissue at the vesicle neck. This was relieved. A Hickey Hare test followed by vasopressin showed no reduction in urinary output. It was also found that with reduction in fluid intake he became rapidly dehydrated and showed marked hyperelectrolytemia. He was followed at home, and at 14 months it was reported that he no longer exhibited polyuria and polydipsia. No other studies could be done.

The author goes on to discuss the different types of polyuria. One type, as seen in chronic renal disease and recovery phase of acute tubular necrosis, is thought to be due to a failure to reabsorb solutes leading to an obligatory loss of water with solute. A second type, as

seen in diabetes insipidus, is due to a lack of antidiuretic hormone or to the failure of the end-organ to respond to antidiuretic hormone. In the third category are a variety of conditions, including hypercalcemic states (do not respond to vasopressin), potassium depletion, various renal tubular defects, and unilateral renal disease. The author feels that his case fits best into the category of nephrogenic diabetes insipidus (of an acquired type) and is similar to the cases reported by Roussak and Oleesky, one of whose cases was likewise a bladder neck obstruction.

Host Influence on Upper Respiratory Flora.—The authors studied the presence of four strains of bacteria in the throats and noses of the members of 38 families. These families were studied monthly over a period of 5 to 21 months, average of 15 months. The bacteria involved in the study were β-hemolytic Streptococcus, H. influenza, Pneumococcus, and H. hemolyticus. Nose swabs were obtained from outer nares. Throat swabs were taken by swabbing the oropharynx and tonsil.

H. influenza was present in all 38 families and present in all members of 27 of the families. Hemolytic streptococci were present in 28 of the families, and in none was it present in all members. Pneumococci and H. hemolyticus were in between the two. The adults did not carry pathogens as abundantly as did the children. One family did not carry any pathogens, even though there were several illnesses during the year.

Hemolytic streptococci were found most often in children between 3 and 9 years of age, almost never under the age of 1 year. H. influenza was similar, except that babies and older people tended to carry it, although not as frequently. The Pneumococcus did not show much variation by age in the throat, but babies most commonly carried it in the outer nares.

Some of the adults were found to carry the Streptococcus most of the time but were not sick. The same was true of H. influenza. The authors speculated as to the reason why babies and young children carried pneumococci in the nose, but not the throat, mentioning either inhibitory factor in noses of adults or possibly the similarity of the epithelial lining (cuboidal) in nose and lower respiratory tract, whereas the oropharynx is lined with squamous epithelium.

The authors felt that the most marked host influence occurred with the hemolytic Streptococcus, the most pathogenic; practically none occurred with the one considered nonpathogenic, H. hemolyticus (showed no variation with age), and the two intermediate ones, pneumococci and H. influenza, were of variable pathogenicity.

The Analgesic Properties of Numorphan (14-Hydroxy Dihydromorphinone): A New Synthetic Narcotic.—This new drug was given to 200 patients, ages 4 to 80 years. All had neoplastic disease. Roughly, 2 mg. of Numorphan was equivalent to 16 mg. of morphine sulfate, 100 mg. of meperidine (Demerol), or 4 mg. of dihydromorphinone (Dilaudid). First effects from subcutaneous injection were felt within 5 to 8 minutes, and full influence, in 10 to 20 minutes. Subjective symptoms were feeling of comfort and body warmth, with indifference to slight noises and discomfort; sleep and the desire to sleep were induced, although the patient could usually be easily aroused. In doses up to 10 mg. (adults) there were no loss in tactile sensation; no nausea, vomiting, or constipation, and no cramps. Analgesia lasted three to six hours.

Toxicity has been chiefly that of respiratory depression and hypotension, usually transient. Addiction may occur. No cumulative toxicity has been found, although not many cases were studied. The advantages over morphine are much greater analgesic properties and lack of gastrointestinal symptoms.

Electrophoretic Analysis of Serum Proteins in Infants and Children: I. Normal Values from Birth to Adolescence.—The authors present data on 159 well infants and children between birth and 13 years of age, including studies of cord blood in 26 infants, 19 of these in the first week. Other age groups were 1 and 2 months, 3 and 4 months, 5 and 6 months, 7 through 11 months, 1 and 2 years, 3 through 5 years, and 6 through 13 years. No one was reported who had had infection within four months. The paper electrophoresis method, which was used, was found to compare very closely with the Tiselius moving-boundary method. Absolute values for total serum globulin and γ-globulin are higher in this series than those of other authors, all of whom used "salting-out methods."

The authors also tested a limited number of infants between three and six months of age by stimulation with diphtheria-tetanus-pertussis immunization. In these infants they could not demonstrate any effect on γ-globulin production.

TABLE 1.—*Results* *

Age Group	Cases, No.	Total Protein		Albumin		α 1-Globulin		α 2-Globulin		β-Globulin		γ-Globulin	
		Mean ±S.E.	Mean ±1.96 S.D.	Mean ±S.E.	Mean ±1.96 S.D.	Mean ±S.E.	Mean ±1.96 S.D.	Mean ±S.E.	Mean ±1.96 S.D.	Mean ±S.E.	Mean ±1.96 S.D.	Mean ±S.E.	Mean ±1.96 S.D.
Mothers at term	26	6.52 ± 0.116	5.32–7.72	39.64 ± 1.096	28.69–50.59	7.20 ± 0.302	4.28–10.32	12.89 ± 0.548	7.41–18.37	21.55 ± 1.359	7.97–35.14	18.64 ± 0.562	13.02–24.26
Babies at birth (cord blood)	26	6.16 ± 0.089	5.36–6.96	50.27 ± 1.636	34.23–66.30	6.42 ± 0.330	3.19–9.66	10.97 ± 0.449	6.58–15.36	11.79 ± 0.927	2.71–20.88	20.59 ± 0.779	12.96–28.22
1 wk. (3–6 days)	19	6.26 ± 0.101	5.39–7.12	49.45 ± 1.418	37.33–61.57	5.61 ± 0.273	3.28–7.93	9.65 ± 0.409	6.16–13.14	16.78 ± 1.786	1.52–32.05	18.51 ± 0.893	10.88–26.15
1 & 2 mo.	13	6.00 ± 0.170	4.80–7.20	56.56 ± 1.693	44.60–68.52	5.23 ± 0.289	3.19–7.28	12.15 ± 0.810	6.43–17.86	14.38 ± 1.00	7.29–21.47	11.68 ± 0.596	7.46–15.89
3 & 4 mo.	13	6.31 ± 0.104	5.57–7.05	59.61 ± 1.860	46.47–72.76	4.27 ± 0.256	2.46–6.08	12.81 ± 0.614	8.47–17.14	15.29 ± 1.175	6.99–23.60	8.02 ± 0.486	4.59–11.46
5 & 6 mo.	11	6.31 ± 0.131	5.46–7.16	54.62 ± 2.414	38.93–70.32	4.84 ± 0.232	3.33–6.35	13.14 ± 1.416	3.93–22.36	16.29 ± 1.160	8.74–23.83	11.10 ± 0.768	6.11–16.09
7 through 11 mo.	15	6.68 ± 0.114	5.82–7.55	51.90 ± 1.246	42.44–61.36	5.66 ± 0.272	3.60–7.72	13.85 ± 0.501	10.05–17.65	16.08 ± 0.638	11.24–20.92	12.57 ± 0.573	8.22–16.92
1 & 2 yr.	20	6.92 ± 0.125	5.83–8.02	54.69 ± 1.663	40.11–69.27	4.93 ± 0.210	3.09–6.78	12.46 ± 0.551	7.62–17.29	14.32 ± 0.697	8.20–20.43	13.60 ± 0.721	7.28–19.91
3 through 5 yr.	18	7.11 ± 0.083	6.40–7.82	50.82 ± 1.207	40.78–60.85	5.07 ± 0.272	2.81–7.33	12.71 ± 0.606	7.67–17.74	15.02 ± 0.671	9.44–20.60	16.38 ± 0.703	10.54–22.23
6 through 13 yr.	24	7.35 ± 0.090	6.48–8.21	54.90 ± 0.972	45.57–64.23	4.74 ± 0.238	2.46–7.03	10.97 ± 0.434	6.80–15.14	13.07 ± 0.411	8.84–17.30	16.31 ± 0.611	10.44–21.18
Adults	10	6.92 ± 0.145	6.02–7.82	52.28 ± 1.186	44.92–59.63	4.37 ± 0.271	2.69–6.05	11.97 ± 0.688	7.70–16.23	13.52 ± 0.578	9.94–17.10	17.91 ± 1.477	8.75–27.07

* All figures expressed as per cent except for total protein. S.E., standard error; S.D., standard deviations; ±1.96 S.D., calculated values occurring between 2.5 and 97.5 percentiles.

TABLE 2.—*Absolute Values for Fractions* *

Age Group	Cases, No.	Serum Albumin	Total Serum Globulin	α 1-Globulin	α 2-Globulin	β-Globulin	γ-Globulin
Mothers at term	26	2.58 (1.65–3.39)	3.93 (3.04–5.62)	0.47 (0.29–0.65)	0.83 (0.48–1.12)	1.42 (0.90–3.26)	1.21 (0.81–1.58)
Newborn infants (cord blood)	26	3.09 (2.06–3.95)	3.08 (1.91–4.28)	0.40 (0.23–0.68)	0.88 (0.38–0.90)	0.73 (0.38–1.63)	1.27 (0.82–1.67)
1 wk. (3–6 days)	19	3.08 (2.27–3.76)	3.17 (2.43–4.35)	0.35 (0.20–0.51)	0.60 (0.36–0.78)	1.06 (0.52–2.83)	1.15 (0.84–1.54)
1 & 2 mo.	13	3.40 (2.76–4.52)	2.60 (1.80–3.34)	0.31 (0.24–0.39)	0.73 (0.44–1.15)	0.86 (0.55–1.48)	0.70 (0.44–0.94)
3 & 4 mo.	13	3.76 (3.09–4.42)	2.55 (1.95–3.63)	0.27 (0.17–0.37)	0.81 (0.57–1.08)	0.97 (0.59–1.76)	0.50 (0.30–0.67)
5 & 6 mo.	11	3.44 (2.82–4.56)	2.87 (2.00–3.71)	0.30 (0.23–0.36)	0.84 (0.41–1.33)	1.02 (0.68–1.33)	0.70 (0.50–0.99)
7 through 11 mo.	15	3.46 (2.72–4.26)	3.20 (2.64–3.88)	0.38 (0.23–0.50)	0.92 (0.75–1.13)	1.07 (0.84–1.29)	0.84 (0.54–1.03)
1 & 2 yr.	20	3.77 (2.91–4.85)	3.15 (1.96–3.95)	0.34 (0.17–0.48)	0.86 (0.58–1.33)	0.99 (0.54–1.35)	0.95 (0.49–1.41)
3 through 5 yr.	18	3.60 (3.10–4.51)	3.48 (2.77–4.37)	0.35 (0.20–0.49)	0.91 (0.59–1.30)	1.07 (0.70–1.61)	1.16 (0.67–1.56)
6 through 13 yr.	24	4.03 (3.45–4.98)	3.32 (2.38–4.39)	0.35 (0.16–0.53)	0.80 (0.48–1.06)	0.96 (0.59–1.34)	1.20 (0.75–1.68)
Adults	10	3.63 (2.87–4.14)	3.29 (2.93–3.48)	0.29 (0.19–0.36)	0.83 (0.64–1.04)	0.94 (0.71–1.14)	1.23 (0.76–1.70)

* Expressed as the mean in gm/100 ml. Figures in parentheses represent range.

Prevention and Control of Postoperative Wound Infections Owing to Staphylococcus Aureus.—The author refers to a previous paper which showed that the postoperative infection rate of clean wounds had increased over a five-year period (1949-1953) at the Massachusetts Memorial Hospital despite the use of prophylactic antibiotics. His data suggested that the increase was due to an abnormally high carrier rate of penicillin-resistant S. aureus as a result of the widespread use of penicillin. He postulated that the routine and extensive use of prophylactic antibiotics in surgery might have an unfavorable effect upon postoperative infection rate. It was his impression that many hospitals were meeting with the same problem and that it was not that more patients were being admitted who had resistant S. aureus but that small epidemics or outbreaks were occurring in hospital patients

in certain specialized situations. He describes a program which he feels has cut down the rate of postoperative infections due to S. aureus.

The routine use of antibiotics was discontinued because the pool of resistant strains in a hospital increases in proportion to the number of patients receiving antibiotics. Bacterial cultures were taken before giving an antibiotic for the treatment of a definite infection. Combinations of antibiotics were used with the idea that less emergence of resistance would occur (this idea is controversial). Because many of the infections were deep-seated, it was felt that the operating room was a big source. Therefore, all personnel were required to wear two masks, which were changed every one and one-half hours during a long procedure, because cultures of the two masks showed that few bacteria were grown from the outer, whereas there were many from the inner one. A full 10-minute surgical scrub with a G-11 soap was used. On the wards face masks were used for doctors, nurses, and patients and gloves were used during changing of septic dressings. Each dressing set was immediately disposed of in a special waxed paper bag. If possible, it is recommended to try and convert an infected wound to a clean one by immediate drainage and debridement, with secondary closure with proper antibiotic coverage. If this is not possible, surgical drainage under strict aseptic precautions and treatment with sodium hypochlorite or saline packs is done. The use of these methods resulted, on the private service, in a significant reduction in major wound infections and also in a reduction of the number of penicillin-resistant S. aureus organisms found. In sampling the staff of the operating room and house surgical floor and operating room patients, a reduction in the carrier rate of Staphylococcus and also a reduction in the rate of penicillin-resistant organisms was found.

Pediatrics, Springfield, Ill.

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A Controlled Study of the Use of Prophylactic Antimicrobials in Premature Infants: Bacteriologic Observations. G. Gialdroni-Grassi, C. V. Prylea, and M. Finland.—p. 899.
* A Controlled Study of the Use of the Bloxsom Air Lock. T. E. Reichelderfer and H. M. Nitowsky.—p. 918.
In-Vitro Response of Enteropathogenic Escherichia Coli to Various Antibiotics. W. I. Metzger and C. J. Jenkins.—p. 929.

Tracheo-Esophageal Fistula Without Esophageal Atresia—Congenital and Recurrent. W. K. Sieber and B. R. Girdany.—p. 935.
The Exposure of Children to Lead. J. Julian Chisolm Jr. and H. E. Harrison.—p. 943.
Hypochromic Microcytic Anemia of Infancy: Iron Depletion as a Factor. H. W. Josephs—p. 959.
American Board of Pediatrics.—p. 979.
Current Problems in Diabetes. R. Klein and Z. Laron.—p. 983.
Mental Deficiency. R. B. Kugel.—p. 997.
Present State of Child Health in Ceylon. C. C. de Silva.—p. 999.
Clinical Conference: A Case for Diagnosis. D. Buchanan.—p. 1013.
Adolescence: Summary of Round Table Discussion. J. Roswell Gallagher and F. P. Heald Jr.—p. 1019.

An Appraisal of Pneumoencephalography in Mental Retardation and Epilepsy.—This is an analysis of the experience with pneumoencephalography on the Pediatric Service of the New York Hospital in which the procedure was done to study patients with mental deficiency and idiopathic epilepsy; the latter is defined as epilepsy in which the history, physical, skull films, electroencephalography, and examination of the spinal fluid do not reveal any etiology. One hundred fifty-one such encephalograms were done, and in this group there were two cases of death directly related to the procedure as well as nine other patients in whom severe reactions accompanied by transient cessation of respiration and other features were noted.

Upon reviewing the amount of useful information derived from these studies a poor correlation between degree of mental retardation and cerebral atrophy was found. Similarly, the findings in cases of epilepsy were of very little value in the management of the patient. The authors, therefore, conclude that with the significant risk involved and the meager amount of useful information obtained pneumoencephalography should be abandoned in the study of patients with mental retardation or idiopathic epilepsy.

A Controlled Study of the Use of The Bloxsom Air Lock.—In a further attempt to evaluate the highly controversial effects of the Bloxsom air lock in resuscitation and management of the newly born, a study was performed at The Johns Hopkins Hospital in which infants born prematurely or with some complication of pregnancy or delivery were randomly alternated between the air lock and the Isolette. The infants were given identical care otherwise as to resuscitative and maintenance measures. There were 72 patients assigned to the air-lock group and 71 treated in the Isolette; those in the air-lock group were allowed to remain in this apparatus for 12 hours and were subsequently transferred to an Isolette. Frequent observations were made of the infants' respirations, color, movements, and secretions during the first 48 hours of life.

Analysis of these data revealed no significant difference in the degree or relief of respiratory distress between the two groups of infants; neither was there a significant difference in over-all mortality rates or in the mortality rates during the first day of life. The authors, therefore, conclude that this series produces no evidence that the air lock is superior in effectiveness as a device for the resuscitation of newly born infants.

Presse médicale, Paris

64, Sept. 29, 1956

* Jaundice After Chlorpromazine (Largactil). F. Lutier, M. Eurin, and J. P. Bos.—p. 1584.

64, Oct. 20, 1956

* New Operative Procedure for Congenital Omphalocele. C. Manoliu-Furnica.—p. 1707.

64, Oct. 24, 1956

* Gargoylism in a Negro Child. W. Berardinelli.—p. 1757.

64, Oct. 31, 1956

* Susceptibility to Anti-Tuberculous Drugs of Bacilli Strains Isolated from Primary Tuberculosis in Children. H. Noufflarde, H. Debre, and S. Foussereau.—p. 1791.

64, Nov. 3, 1956

* Indirect Appraisal of the Contagiousness of Pulmonary Tuberculosis Treated with Isoniazid by Study of the Source of Infection of Primary Tuberculosis in the Child. M. Kaplan, R. Grumbach, and B. Dobrowolski.—p. 1809.

64, Nov. 7, 1956

* Efficacy of BCG. Andre Plichet.—p. 1852.

64, Nov. 17, 1956

Theoretical and Practical Problems of Left-Handedness in Children. J. de Ajuriaguerra and R. Diatkine.—p. 1905.

64, Nov. 21, 1956

* Liver Puncture in Eczema. C. Huriez, F. Desmons, M. Benoit, and P. Martin.—p. 1956.

64, Dec. 1, 1956

Study of an Epidemic of E. Coli 0111.; B4 in Relation to Bacteriophage Typing and Bacterial Resistance. Paul Monnet and Pierre Nicolle.—p. 2017.

64, Dec. 15, 1956

Clinical Significance of Hyperaminoaciduria: Review. Bernard Pepin.—p. 2091.

Jaundice After Chlorpromazine (Largactil).—The authors report a case of obstructive jaundice occurring one week after the last dose of chlorpromazine given for 19 days. Remissions of the jaundice occurred on the 7th and 30th days but were brief. Peritoneoscopy showed a normal reddish color to the liver and a slightly distended gallbladder in the sixth week of the jaundice. Cholecystectomy was performed because of cystic duct dystonia, and the jaundice gradually cleared. A liver biopsy showed thrombi and stasis in the smaller canaliculi. The authors note that in other reported cases of jaundice after chlorpromazine surgery has been resorted to in two out of three cases because of the obstructive nature of the jaundice.

New Operative Procedure for Congenital Omphalocele.—The author reports an ingenious operation whereby the costal cartilage is removed along the costal margin, brought forward over the abdomen, and used as a support in repairing the defective abdominal wall. He reports a 17-year-old patient cured by repair in this fashion.

Gargoylism in a Negro Child.—The author reports a case in a 5-year-old Negro boy and also reports a case of a new syndrome he believes has some traits in common with gargoylism, in a 2-year-old white boy who showed a bone age of 5 to 6 years, acromegaly of the legs, abnormal position of the anus, hepatosplenomegaly cirrhosis, hyperlipemia, hyperproteinemia, elevated glucose-tolerance curve, and enlargement of the penis but no other signs of precocious puberty. Irradiation of the hypophysis in this latter case reduced the size of the liver and spleen and brought the blood lipids to normal. The hyperproteinemia continued, but the musclature became more normal. The author believes with Ernoult that gargoylism may be due to excessive secretion of the pituitary somatotropic hormone associated with thyroid deficiency.

Susceptibility to Anti-Tuberculous Drugs of Bacilli Strains Isolated From Primary Tuberculosis in Children.—Four hundred thirty strains of tubercle bacilli were tested with streptomycin, 219 strains with isoniazid, and 217 strains with PAS. The following points were observed. No case of development of resistance to streptomycin has been found since 1952 in children treated for primary or secondary tuberculosis. Resistance to streptomycin was noted in four cases in children who had not been treated with the drug. Five strains of the 219 studied were found resistant to isoniazid; one of these was a case of bovine tuberculosis and the other four were found in children who had been treated with isoniazid before study. One case of resistance to PAS was found. Strains which are resistant to INH are less virulant for guinea pigs and possibly less virulent for man.

Indirect Appraisal of the Contagiousness of Pulmonary Tuberculosis Treated With Isoniazid by Study of the Sourse of Infection of Primary Tuberculosis in the Child.—The authors were interested in the problem of whether children exposed to streptomycin- and PAS-treated cases of tuberculosis were more liable to primary infection than when exposed to adults treated with isoniazid (INH). They found no difference in the degree of contagiousness of adults treated with INH and those given streptomycin and PAS, and they therefore conclude that INH does not result in qualitative changes in tubercle bacilli

making them less virulent for children. One should therefore strictly separate children who have not received BCG from contact with tuberculous adults, and not depend upon the effect of the adult's treatment to protect the child.

Efficacy of BCG.—The author reviews two school epidemics of tuberculosis, one reported in *Acta tuberculosa scandinavica* (32:89, 1956) and one reported in *Schweizerische medizinishe Wochenschrift* (No. 41, Oct. 13, 1956). In the first epidemic, in 1943, 368 girls between the ages of 12 and 18 years were exposed to a serious case of tuberculosis. A few months previously 105 had been noted to have a negative tuberculin test (not having received BCG), 133 had a positive tuberculin test after BCG vaccination in 1942, and 130 had a positive tuberculin test from previous natural infection. Of the 105 children with negative tuberculin tests, 94 were exposed to the infection; 41 of these developed an obvious primary infection, and 14 developed progressive pulmonary tuberculosis after a latent period of up to 10 years. Of the 133 children vaccinated with BCG, 106 were exposed to the infection; none of these had an evident primary infection, and 2 of the 106 developed progressive pulmonary tuberculosis. Of the 130 children who had a "natural infection positive tuberculin," 105 were exposed to the infection and 9 developed progressive pulmonary tuberculosis in the eight years that followed, although 3 of these could possibly have been from another exogenous source of reinfection. Thus the rate of progressive tuberculosis in children with negative tuberculin tests exposed to an open case was 15%; in those previously vaccinated with BCG it was 1.9%, and in children with a positive tuberculin test due to previous human infection the rate was between 5.6 and 8.5%.

In the Swiss epidemic period there were 34 children, 5 of whom had received BCG, none of whom became ill, and among the 29 who had not been previously vaccinated, and in whom the state of the tuberculin test was not known prior to the epidemic, 21 became ill and required, collectively, 234 months of hospitalization, i. e., a quarter of a year per child. Two families each had two children in the exposed class, one of whom had been given BCG and the other not. The two vaccinated children remained well, and the two others, who had not received BCG, became ill.

The author adds a third illustrative situation from France, in which 32 children given BCG in December, 1954, were exposed from January to March, 1955, to an open case of tuberculosis. X-ray study of all these children in May, 1955, and January, 1956, has shown no signs of tuberculosis in any child.

Liver Puncture in Eczema.—The authors performed liver puncture in 44 cases of eczema and found very little alteration in cases of constitutional or sensitization eczema, but in cases of toxic dermatitis due to local or general medications, especially after metallotherapy, serious alteration and even necrosis of liver cells was frequently found.

Radiology, Syracuse, N. Y.

67, Dec., 1956

* Pseudohypoparathyroidism. Joseph V. Cusmano, David H. Baker, and Nathaniel Finby.—p. 845.

Pseudohypoparathyroidism.—Pseudohypoparathyroidism (Seabright bantam syndrome) is a familial disease of metabolism differing from other forms of chronic hypoparathyroid tetany in that the parathyroid glands, apparently normal in structure, do not give a normal response to the parathyroid hormone.

Elrick, Albright, et al., from a collection of 14 cases, emphasized the following features of the disease:

1. Clinical and laboratory evidence of chronic parathyroid insufficiency; tetany without evidence of renal disease, steatorrhea, or osteomalacia, with little or no response to parathormone.

2. Shortening of the metacarpals (first, fourth, and fifth) and metatarsal bones (first and fifth). (Involved bones are frequently widened and show lack of prominence of knuckles in the clenched fist.)

3. Shortness of stature, thickset appearance, round facies, mental retardation, and short stubby fingers.

4. Soft-tissue calcification involving the basal ganglia and subcutaneous tissues.

The authors add six cases: female twins, age 12 years; a male, 19 years; a female, age 10 to 28 years; a female, 11 years, and a female, 5½ years. The age of involvement has varied from 16 months to 49 years. There has been no significant sex variation. Four of the authors' six patients were Jewish.

Symptomatology was related predominantly to episodes of hypocalcemia. Tetany, with manifestations of stridor, muscular hyperexcitability, tonic convulsions, tingling, and cramps of the extremities, was seen at some time in every patient with this disease.

This rare familial disease is made up of three components: first, the metabolic defect manifest as a failure to respond to parathormone; second, bone dysplasia; third, extraskeletal calcification and ossification. The roentgen findings of short metacarpals, thickened calvarium, extracalcification in soft tissue, singly or in combination, in patients with symptoms of parathyroid insufficiency should suggest the diagnosis of pseudohypoparathyroidism.

Metabolism, New York

5, No. 6 (Nov., Pt. 2) 1956

* Symposium on Clinical and Experimental Effects of Sulfonylureas in Diabetes Mellitus.
Editorial statement. Rachmeil Levine and Garfield G. Duncan.—p. 721.
Studies on the Site of Action of the Arylsulfonylureas in Man. Albert E. Renold, Albert I. Winegrad, E. Rudolf Froesch, and George W. Thorn.—p. 757.

Symposium on Clinical and Experimental Effects of Sulfonylureas in Diabetes Mellitus.—Three preparations capable of being administered orally have been studied intensively over the past 15 years in order to determine if they have a place in the treatment of diabetes mellitus, thus possibly replacing insulin, which has to be given by injection. The three preparations are (1) *p*-aminobenzolsulfonamide isopropylthiodiazol (IPTD); (2) 1-butyl-3-sulfanilurea (B2-55, Carbutamide), and 1-butyl-3-*p*-tolylsulfonylurea (U 2043, Orinase, Tolbutamide).

There is general agreement that, in certain kinds of "adult-onset" diabetes the drugs can decrease the hyperglycemia and glycosuria. The maintenance dose is between 1 and 2 gm. daily, and the new drugs therefore may replace 20 to 40 units of insulin. On the other hand, in juvenile diabetics the drugs are usually without effect. The explanation for this difference between adult and juvenile types of diabetes may be that, whereas in "adult onset" diabetes the insulin content of the pancreas averages about 30% of normal, in juvenile diabetics this percentage is close to zero, hardly ever exceeding 10%.

The opinion that the new drugs are ineffective in the absence of insulin gains support from the fact that they are also ineffective in humans who have undergone pancreatectomy.

The mechanism of action of the new drugs has not yet been determined with certainty. There is some agreement that they do not act by damaging glucagon excretion by the alpha-cells or by depressing the insulin antagonism exerted by the hypophysis or adrenal glands. There is some evidence (which is not conclusive) that they inhibit the formation of glucose from its precursors in the liver and that they may counteract insulinase. Possibly, they may stimulate the beta-cells to secrete insulin. There is no evidence that they have any insulin-like activity.

The new drugs seem to be relatively free from major toxic side-effects. Dermatitis, leukopenia, and depression of iodine uptake by the thyroid gland have been reported, however.

It appears that the major benefit to be expected from the use of these new drugs is in the treatment of those patients in whom the diabetes could probably be controlled by dietary measures and reduction in body weight. (About 80% of adult diabetics are estimated to be overweight when first seeking treatment). Their usefulness would appear to be greatest in patients who have difficulty with dietetic management. The drugs are ineffective in dealing with acute complications such as infection and trauma and also in juvenile diabetes, as noted above.

News and Comment

ANNOUNCEMENTS

Institutes in Care of Premature Infants.—The Institutes for Physicians and Nurses in the Care of Premature Infants at the New York Hospital-Cornell Medical Center, under the sponsorship of the New York State Department of Health and the United States Children's Bureau, will begin their ninth year of operation in the fall of 1957. These Institutes are designed to meet the needs of physicians and nurses in charge of hospital premature nurseries and special premature centers and of medical and nursing directors and consultants in state and local premature programs. The attendance at each Institute is limited to six physician-nurse teams. The program for physicians is of two weeks' duration, and that for nurses, of four weeks' duration. Participants pay no tuition fee, and stipends are provided to help cover expenses during attendance at the Institute. Institutes for the 1957-1958 year are scheduled to start on the following dates: Sept. 30, 1957; Nov. 18, 1957; Jan. 6, 1958. In addition, if the number of applicants is sufficient to warrant it, fourth and fifth Institutes will be scheduled, beginning March 3, 1958, and late in April or May, 1958. Early application for these Institutes is essential, since plans are contingent on the number of applications received. Additional information may be secured by writing Box 143, Institute in the Care of Premature Infants, The New York Hospital, 525 E. 68th St., New York 21.

Fifth International Congress of Internal Medicine.—The International Society of Internal Medicine has announced that its Fifth International Congress of Internal Medicine will be held at the new Sheraton Hotel, Philadelphia, April 24-26, 1958. This will be the first meeting of the Society outside of Europe. In making the announcement, the International Society's President, Sir Russell Brain, who is also President of the Royal College of Physicians of London, said, "The Executive Committee of the Society has chosen the United States for its Fifth Congress in response to an invitation extended by the American College of Physicians and with the objective of securing greater American participation in its deliberations and of allowing foreign members, at first hand, to learn more about American developments in the medical sciences."

The previous Congresses, at two-year intervals, were held in Paris, London, Stockholm, and Madrid. At those meetings, however, the United States, as well as many other nations throughout the world, was represented. The present membership of the Society, including 48 nations, is about 3000.

This Society, the only international one embracing all aspects of internal medicine, was organized in 1948, largely at the instigation of Prof. Nanna Svartz, of Stockholm, the physician to the King of Sweden. It was her contention that the various branches of internal medicine should be kept in touch with one another, as is accomplished in North America by the American College of Physicians, and that this should be done on a truly international basis. She also emphasized the importance of purely personal and nonpolitical contacts among physicians of different countries.

The objectives of the Society, as stated in its Statutes, are "to promote scientific knowledge in internal medicine, to further the education of the younger generation and to encourage friendship among physicians of all countries." The members are "specialists in internal diseases, acknowledged as such and accepted by the appropriate national societies of internal medicine."

The first president of the International Society was Prof. A. Gigon, of Basel, Switzerland. He was succeeded, in 1952, by Dr. Svartz, and she, by Sir Russell Brain, the President of the Royal College of Physicians of London.

At the Philadelphia Congress it is planned, through lectures and panels, to analyze medical achievements of world-wide significance, to evaluate certain apparent problems, and to chart courses of action designed to enhance technical knowledge and to aid in the continuing war against disease. At the same time, the plan includes such social and cultural activities as will tend to promote cooperation, friendship, and mutual understanding among physicians and peace among their countries.

The 1958 Annual Session of the American College of Physicians will occur in Atlantic City, April 28 to May 2, immediately following the Philadelphia Congress. The members of the Congress are invited to attend all the scientific programs and extensive exhibits (the foreign members on a purely courtesy basis). Also, those members of the Society who make an early reservation and advance payment may join certain Fellows of the College on its customary postconvention cruise to a near-by foreign country. Tours throughout the United States may be arranged through an approved travel agency.

T. Grier Miller, M.D., Philadelphia, is the President of the Congress; Edward R. Loveland, F. A. C. P. (Hon.), Philadelphia, is the Secretary-General, and Mr. J. Malcolm Johnston, Philadelphia, the Treasurer.

The Executive Committee consists of Frank N. Allan, M.D., Boston; Mr. J. Malcolm Johnston, Philadelphia; Chester S. Keefer, M.D., Boston; Mr. Edward R. Loveland, Philadelphia; William S. Middleton, M.D., Washington, D.C.; T. Grier Miller, M.D., Philadelphia; Walter L. Palmer, M.D., Chicago; Howard A. Rusk, M.D., New York; Wallace M. Yater, M.D., Washington, D. C.

The Program Committee includes Frank N. Allan, M.D., Chairman, Boston; Philip S. Hench, M.D., Rochester, Minn.; Carl V. Moore, M.D., St. Louis; Albert M. Snell, M.D., Palo Alto, Calif.; Irving S. Wright, M.D., New York.

Postgraduate Course in Pediatric Allergy.—New York Medical College, Flower and Fifth Avenue Hospitals, Division of Graduate Studies, Department of Graduate Pediatrics, announces a postgraduate course in pediatric allergy, to be held under the direction of Bret Ratner, M.D., Professor of Clinical Pediatrics and Associate Professor of Immunology. The course will meet for 30 sessions, Nov. 6, 1957, to May 28, 1958, on Wednesdays, 9 a.m. to 4 p.m. The fee is $300.

The course consists of lecture-seminars, laboratory and clinical procedures, clinic work, and animal experimentation covering basic principles of diagnosis and treatment of allergy and applied immunology in children.

Applicants must be certified in pediatrics or have the requirements for certification. A limited number of allergists practicing with adults may also apply. Applications should be made to Office of the Dean, New York Medical College, 5th Ave. at 106th St., New York 29.

Fellowships in Pediatric Psychiatry.—Two fellowships have been made available by the United States Public Health Service for training in pediatric psychiatry at the State University of New York. The program will be under the direction of Dr. Alfred M. Freedman.

The fellowships are one year in duration, and salary depends upon extent of training. These fellowships have been established to give a physician who has training in pediatrics one year's experience in the psychiatric aspects of pediatric practice. Fellows may begin their training on July 1, 1957, or thereafter. They must be citizens of the United States or have declared their intention to become citizens.

Through clinical work and participation in seminars, the fellow will gain knowledge of the interrelationship of emotional and social factors and physical illness. The fellow will also have the opportunity to participate in the research program of the Pediatric Psychiatry unit, which currently is concerned with long-range developmental studies of prematurely born children, varying aspects of brain damage, and biological aspects of mental illness. The fellow will also have an opportunity to be involved in other activities of the Department of Pediatrics.

Communications in regard to these fellowships should be addressed to Richard L. Day, M.D., Professor of Pediatrics, State University of New York College of Medicine at New York City, 450 Clarkson Ave., Brooklyn 3, N. Y.

Scientific Sessions of American Heart Association to Honor William Harvey.—The Thirtieth Scientific Sessions of the American Heart Association, to be held in Chicago's Hotel Sherman, Friday, Oct. 25 through Monday, Oct. 28, will commemorate the 300th anniversary of the death of William Harvey, English scientist who discovered the circulation of the blood. To honor William Harvey, a special exhibit and a film showing his work are planned. There will also be a brief dedication ceremony on Saturday morning, when the regular Scientific Sessions get under way.

On Saturday morning a general session will feature presentation of the Albert Lasker Award of the American Heart Association and the Lewis A. Conner Memorial Lecture, to be delivered by Dr. Charles W. Rammelkamp Jr., Professor of Medicine, Western Reserve University, who has made outstanding contributions in the field of streptococcal control and pre-

vention of rheumatic fever. The Saturday afternoon program includes Special Sessions of the Association's Section on Clinical Cardiology and Section on Circulation and of the Council on Rheumatic Fever and Congenital Heart Disease.

General Sessions on Sunday will include in the morning the George E. Brown Memorial Lecture, to be delivered by Dr. Nelson W. Barker, Professor of Medicine, Mayo Foundation, who is one of the leading clinicians in the field of peripheral vascular disease, and in the afternoon a panel on "The Present Status of Fat Metabolism and Atherosclerosis," sponsored by the Council on Community Service and Education.

The Association's Annual Dinner, at which a number of awards will be presented, will take place on Sunday.

Special Sessions of the Section on Basic Science and Section on Cardiovascular Surgery and of the Council for High Blood Pressure Research will conclude the Scientific program on Monday at noon.

Six panel sessions of the Association's Assembly will be held on Monday. The full Assembly, the American Heart Association's national delegate body, will meet Tuesday morning to review panel recommendations and to elect officers of the Association and Board members.

GENERAL NEWS

American Heart Association Issues Throat Culture Statement.—To emphasize the importance of throat cultures in cases of streptococcal or suspected streptococcal infections, the control of which is important in preventing rheumatic fever, the American Heart Association has issued a new statement entitled "A Method for Culturing Beta Hemolytic Streptococci from the Throat."

The statement was prepared by Lewis W. Wannamaker, M.D., at the request of the Association's Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, for use by physicians, directors of laboratories and their staffs, health departments, and public health and hospital nurses.

The statement is a companion piece to the leaflet "Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections." Single copies of both publications are available free from the American Heart Association or local Heart Associations.

Rheumatic Fever Symposium Issued.—The American Heart Association has combined three review articles by outstanding medical authorities into a publication entitled "Symposium on Rheumatic Fever." The three papers, which originally appeared as a symposium in the December, 1956, issue of the Association's professional journal, *Circulation*, are "The Nature of Rheumatic Fever," by Dr. Maclyn McCarty; "Prophylaxis of Rheumatic Fever," by Dr. Edward A. Mortimer and Dr. Charles H. Rammelkamp Jr., and "Treatment of Rheumatic Fever," by Dr. E. G. L. Bywaters.

Physician's Manual on Congenital Cardiac Defects Published.—The American Heart Association has issued a new booklet entitled "Congenital Cardiac Defects—A Physician's Guide for Evaluation and Management." The publication was prepared by the Committee on Congenital Heart Disease of the Association's Council on Rheumatic Fever and Congenital Heart Disease, Ruth Whittemore, M.D., Chairman.

Designed primarily for the physician who is not a cardiologist, the twenty-seven-page booklet will help doctors who encounter patients with congenital malformations of the heart to decide whether and when such patients should have special studies done in a cardiac center or by a cardiologist familar with these problems.

The Association has also issued a report setting standards for services and equipment in centers responsible for the diagnosis and surgical care of patients with congenital defects of the heart and blood vessels. The report, entitled "Standards for Centers Caring for Patients with Congenital Cardiac Defects," appeared originally in the April, 1956, issue of the Association's professional journal *Circulation* and is of particular interest to directors of centers concerned with diagnosis and surgery for patients with congenital cardiac defects. The report was prepared by the American Heart Association's Subcommittee on Education and Standards in the Field of Congenital Heart Disease.

Single copies of both pamphlets are available free from the American Heart Association or from local Heart Associations.

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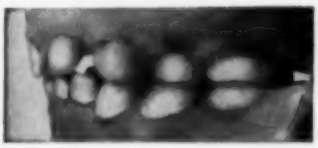

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